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RESPIRATORY CARE

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40TH YEAR—ESTABLISHED 1956

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- Evaluation of Pulse-Dose and Continuous-Flow Oxygen
- Responses to Inhaled Bronchodilator
- Multisite Evaluation of a Hemoglobin-Based Control
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Editorials, Reviews, and Commentaries To Note

Childhood- versus Adult-Onset Asthma (NHLBI Workshop Summary)—W Busse, SP Banks-Schlegel, GL Larsen. Am J Respir Crit Care Med 1995;151:1635-1639.

The Assessment and Management of Adults with Status Asthmaticus (State of the Art)—TC Corbridge, JB Hall. Am J Respir Crit Care Med 1995;151:1296-1316.

How Detrimental Is Chronic Use of Bronchodilators in Asthma and Chronic Obstructive Pulmonary Disease? (Commentary)—CP VanSchayck, SGM Clooserman, ID Hofland, CLA VanHerwaarden. Am J Respir Crit Care Med 1995;151:1317-1319.

Is the Routine Use of Inhaled β-Adrenergic Agonists Appropriate in Asthma Treatment? YES and NO(editorials)— **YES:** A Wanner. Am J Respir Crit Care Med 1995;151:597-599. **NO:** MR Sears. Am J Respir Crit Care Med 1995;151:600-601.

Monitoring Cardiopulmonary Resuscitation: Role of Blood and End-Tidal Carbon Dioxide Tension (editorial)—JD Gasman, RS Fishman, TA Raffin. Crit Care Med 1995;23(5):799-800.

Sleep in the Intensive Care Unit—SL Krachman, GE D'Alonzo, GJ Criner. Chest 1995;107 (6):1713.

The most critically ill patients in the hospital are located in the ICU. Due to intensive individualized care and monitoring, these patients often suffer from severe sleep deprivation. The amount and continuity of sleep as well as normal sleep architecture are all affected. Moreover, by impairing protein synthesis, cell division, and cellular immunity, sleep deprivation can affect the healing process and thus contribute to an increased morbidity and mortality. Reasons for sleep deprivation appear to be multifactorial and include the following: the patient's chronic underlying illness, an acute superimposed illness or surgical procedure, medications used in treatment of the primary illness, and the ICU environment itself. Therapeutic interventions need to address each of these potential causes, with an emphasis placed on providing an environment that is both diurnal and focused on the importance of uninterrupted sleep. *See related editorial: **The Disruptive ICU: An Issue to Lose Sleep Over?**—SE Eveloff. Chest 1995;107(6):1483-1484.*

Pulmonary Barotrauma and Related Events in Divers—LW Raymond. Chest 1995;107 (6):1648.

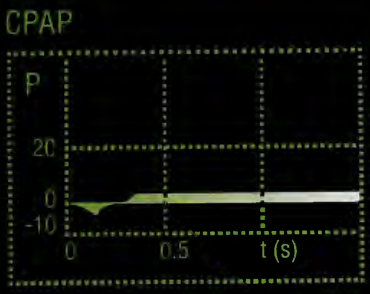
Although pulmonary barotrauma (PBT) is a well-known clinical entity, its recognition in divers is sometimes delayed and its implications for future diving often are unappreciated. The pulmonary complications of diving activities range from mere discomfort from mediastinal emphysema or pneumothorax, or both, to life-threatening gas embolization. In nine cases described here, only minor manifestations were associated with PBT which occurred at or close to the surface; but three of the four divers [who developed minor manifestations, explanation added] were found to have abnormal pulmonary function. More serious manifestations resulted from PBT which took place at depths of 16 to 120 ft. Even minor forms of PBT should be considered a contraindication to further diving, since they are prone to recur. Such recurrences—even at shallow depths—may cause serious complications.

Cerebral Air Embolism in Asthmatic Scuba Divers in a Swimming Pool—LD Weiss, KW Van Meter. Chest 1995;107(6):1653.

Significant shallow-water injuries can occur in scuba divers, even in swimming pools. Two asthmatic patients are presented who sustained cerebral air emboli during Scuba classes in a swimming pool. Such injuries may be more common in asthmatics. Asthma is a contraindication to Scuba diving.

Endotracheal Intubation by Paramedics during In-Hospital CPR—JR Smale, K Kutty, J Ohlert, T Cotter. Chest 1995;107(6):1655.

STUDY OBJECTIVE: To examine whether well-trained paramedics can perform emergent, successful, uncomplicated, endotracheal intubations during in-hospital cardiopulmonary resuscitation (CPR). DESIGN: Retrospective review of medical records of inpatients undergoing emergent, endotracheal intubations during in-hospital CPR over 8 months, with comparison of the performance of the paramedics against that of other hospital-based personnel. SETTING: A 437-bed Midwestern community teaching hospital. PATIENTS: Adult inpatients in general medical/surgical wards. MAIN OUTCOME MEASURES: The rapidity of response of paramedics and other medical personnel to a cardiorespiratory arrest (Code 4) announcement, and reported difficulties, success rate, rapidity, and complications of endotracheal intubation. RESULTS: In the 47 cardiorespiratory arrests requiring intubation that we analyzed, the median response times (with values in parentheses representing interquartile range [IQR]) for paramedics, nurse anesthetists (CRNAs), anesthesiologists, and other physicians respectively, were 2.00 (4.25), 4.00 (2.0), 4.00 (15.0), and 7.00 (8.0) min, requiring a median of 1.0 attempt for all groups (mean values, 1.4, 1.125, 1.0, and 1.4 respectively) to place an endotracheal tube. The paramedics were successful in 13 of 15 instances. Median times (seconds) required for intubation by various groups (same order as response times, with IQR given in parentheses) were 60 (30), 150 (270), 45 (30), and 60 (30). Difficulties were reported by all groups, including patients' resistance to intubation, airway obstruction by extraneous material, and difficulty in visualizing the glottis. Reported complications (4%) were confined to groups other than the paramedics. CONCLUSIONS: Paramedics can successfully, and with-



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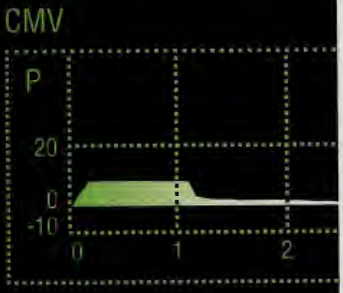

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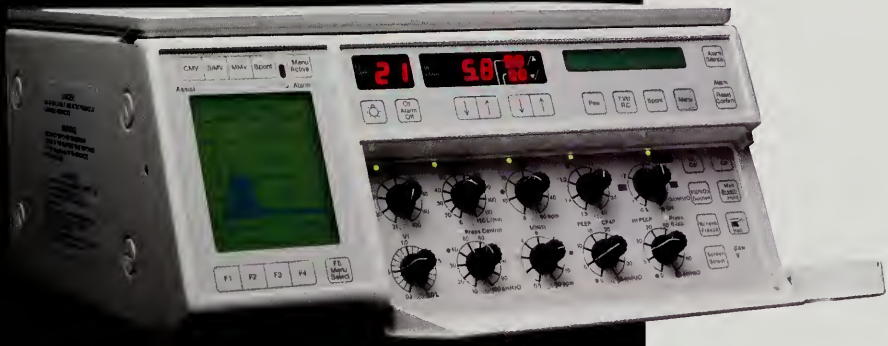

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out undue difficulty or complications, place endotracheal tubes during in-hospital CPR. Appropriately trained paramedics may be incorporated into hospital-based CPR teams in two contexts: (1) to provide an acceptable, long-term solution to the scarcity of personnel highly skilled in endotracheal tube placement during in-hospital CPR, and (2) to fulfill the need for hospitals to have on-site, qualified professionals to perform emergent endotracheal intubation during CPR. In the latter situation, personnel skilled in airway management could supplement the paramedics on demand. Further investigation in this area could be fruitful in view of the small sample size covered in this study.

Radiologic Evaluation of Emphysema in Patients with Chronic Obstructive Pulmonary Disease: Chest Radiography versus High Resolution Computed Tomography—M Miniati, E Filippi, F Falaschi, L Carrozzi, ENC Milne, HD Sostman, M Pistolesi. Am J Respir Crit Care Med 1995;151:1359.

To objectively reappraise the role of the chest radiograph (CXR) in the clinical assessment of emphysema, we compared a standardized reading of CXR with both a visual scoring and a quantitative analysis of high resolution computed tomography (HRCT) of the chest in 46 consecutive patients with chronic obstructive pulmonary disease (COPD) and fixed expiratory airflow limitation. CXR were scored for signs of overinflation and pulmonary vascular deficiency by three independent observers. HRCT scans were independently scored for extent of emphysema and for both severity and extent of emphysema. In 28 of 46 patients, inspiratory and expiratory HRCT scans were analyzed quantitatively by measuring the mean CT number in Hounsfield Units (HU) and the percentage of lung area with CT numbers < -900 HU. Quantitative CT data were compared with reference values obtained in seven normal nonsmokers. The CXR score of emphysema showed a highly significant interobserver reproducibility and correlated linearly ($p < 0.001$) with HRCT visual scores and quantitative data from both inspiratory and expiratory CT scan. CXR score correlated with functional indices of airflow obstruction, overinflation, and impaired lung diffusing capacity in a way comparable to that obtained by using qualitative and quantitative CT data. Patients with no signs of emphysema on CXR had mean expiratory CT numbers within normal range and a fraction of lung area with CT numbers < -900 HU on expiratory scan not exceeding 15% of total cross-sectional area. The latter value was consistently greater than 15% in patients with CXR score > 0. Lung function impairment was significantly less severe ($p \leq 0.0001$) in patients with CXR score $= 0$ than in those with CXR score > 0. For the clinical evaluation of emphysema, the information derived from standardized reading of CXR is comparable to that obtained by qualitative and quantitative analysis of HRCT.

Which Index of Peak Expiratory Flow Is Most Useful in the Management of Stable Asthma?—HK Reddel, CM Salome, JK Peat, AJ Woolcock. Am J Respir Crit Care Med 1995;151:1320.

Calculation of diurnal peak expiratory flow (PEF) variability using values before and after bronchodilator is no longer possible for many asthmatic patients because they now use β-agonists as needed for symptoms rather than regularly. This study assesses the usefulness of a number of alternative PEF indices as markers of airway lability in subjects with stable, although not necessarily well-controlled, asthma. Forty-six adult subjects completed a questionnaire about symptoms and treatment in the previous 3 mo. Spirometric function and airway hyperresponsiveness (AHR) were assessed; AHR was expressed as dose response ratio (DRR) (maximal percent fall in FEV_1 divided by final dose of histamine). Subjects recorded PEF morning and evening, before and after bronchodilator (if used) for 2 wk. Nine different PEF indices were calculated. Diurnal variability (amplitude percent maximum) without bronchodilator was significantly less than diurnal variability with bronchodilator. Normal indices of PEF lability were found in 42% of subjects with reduced maximal midexpiratory flow (MMEF). Most of the PEF indices correlated strongly with DRR, and less strongly with symptom score and airway obstruction. Minimum morning prebronchodilator PEF over a week (expressed as percent recent best or percent predicted) is recommended as the best PEF index of airway lability in patients with stable asthma because it correlates strongly with AHR, patients are more likely to comply with a once-daily reading, the calculation is simple, and regular use of a β-agonist is not required.

A Prospective Study of Diet and Adult-Onset Asthma—RJ Troisi, WC Willett, ST Weiss, D Trichopoulos, B Rosner, FE Speizer. Am J Respir Crit Care Med 1995;151:1401.

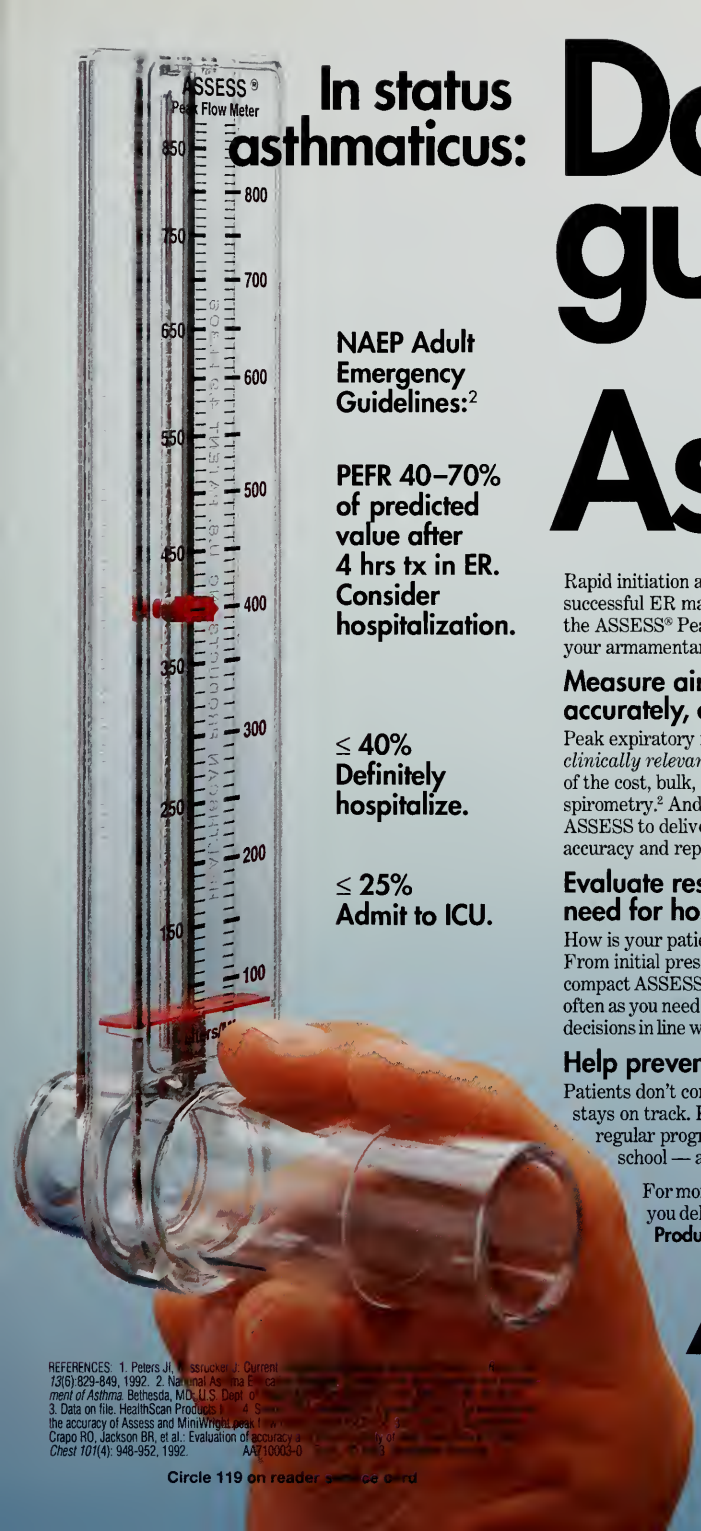
A role for diet in the pathophysiology of asthma may be mediated by altered immune or antioxidant activity with consequent effects on airway inflammation. We evaluated associations between several dietary factors assessed by a semiquantitative food frequency questionnaire, and incidence of asthma over a 10-yr period in 77,866 women 34 to 68 years of age. Women in the highest quintile of vitamin E intake from diet, but not from supplements, had a risk of 0.53 (95% confidence interval [CI] = 0.33 to 0.86) compared with women in the lowest quintile. This relationship, however, was attenuated when the contribution from nuts, a major source of vitamin E in these data and a possible allergen, was removed (relative risk = 0.74 [0.50 to 1.10], p for trend = 0.007). Positive associations were found for vitamins C and E from supplements, but appeared to be explained by women at high risk of asthma initiating use of vitamin supplements prior to diagnosis. A nonsignificant inverse association with carotene intake was noted, but no clear relations with asthma were demonstrated for intake of linoleic acid or omega-3 fatty acids. These data suggest that antioxidant supplementation and intake of various fats during adulthood are not important determinants of asthma, although vitamin E from diet may have a modest protective effect.

Plasma Elastase Levels and the Development of the Adult Respiratory Distress Syndrome—SC Donnelly, I MacGregor, A Zamani, MWG Gordon, CE Robertson, DJ. Steedman, K Little, C Haslett. Am J Respir Crit Care Med 1995; 151:1428.

Inflammatory cells, particularly neutrophil granulocytes, have been implicated in the pathogenesis of the adult respiratory distress syndrome (ARDS). In this study, we investigated whether a relationship exists between neutrophil elastase in the plasma of multiple-trauma patients on initial hospital presentation and the subsequent development of lung injury and ARDS. Sixty-one multiple-trauma patients were enrolled prospectively. Neutrophil elastase was measured by a specific radioimmunoassay, and analysis was performed by nonparametric statistical methods. A highly significantly elevated plasma elastase level was found in patients who progressed to ARDS (median 217 ng/mL, range 127 to 480) ($n = 8$) compared with those who did not (median 117 ng/mL, range 21.4 to 685) ($n = 53$) ($p = 0.009$). Significant correlation was found between initial elastase values and subsequent requirement for mechanical ventilation ($p = 0.01$), lowest arterial oxygen saturation/oxygen supplementation recorded ($p = 0.003$), and organ failure score ($p = 0.006$). This study shows that within minutes of the initiating trauma event, there is evidence of enhanced neutrophil degranulation as manifested by elevated levels of immunoreactive neutrophil elastase in the peripheral blood. The level of this enzyme correlates with the degree of subsequent lung injury and ARDS. These findings reinforce the importance of neutrophils and their secretory products in early ARDS disease pathogenesis.

Myocardial Injury in Critically Ill Patients: A Frequently Unrecognized Complication—TM Guest, AV Ramanathan, PG Tuteur, KB Schechtman, JH Ladenson, AS Jaffe. JAMA 1995;273 (24):1945.

OBJECTIVE: To determine the incidence and effect of unrecognized cardiac injury in critically ill patients. DESIGN: Prospective blinded, single-center study. SETTING: The medical and respiratory intensive care unit of an academic health center. PATIENTS: Two hundred nine patients



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(224 admissions). MAIN OUTCOME MEASURES: Daily measurement of levels of cardiac troponin I, a sensitive, highly specific, and long-lived marker of myocardial injury. Concurrently signs and symptoms potentially related to myocardial ischemia were tabulated by blinded investigators All clinical evaluation and management decisions were made by the physicians responsible for the care of the patient. RESULTS: Thirty-two (15%) of the 209 patients had evidence of myocardial damage based on elevated levels of cardiac troponin I. Only 12 (37%) of these 32 patients were diagnosed as having acute myocardial infarction by the intensive care unit staff. Cardiac damage was unrecognized in the other 20 (63%). Unrecognized cardiac injury was more common in young patients and in blacks. Mortality in patients with myocardial injury that was recognized (42%) or unrecognized (40%) was higher than in those without myocardial injury (15%) ($P < 0.001$). Patients with cardiac injury were more frequently hypotensive (75% vs 50%; $P = 0.007$) and in need of mechanical ventilation (66% vs 27%; $P < 0.001$) and had longer intensive care unit stays (5.3 vs 3.1 days; $P < 0.007$) than patients without cardiac injury. CONCLUSION: The incidence of myocardial injury defined by elevated levels of cardiac troponin I was unexpectedly high and associated with increased morbidity and mortality. Clinically, it was often unrecognized.

Nasal Route for Infant Resuscitation by Mothers—SL Tonkin, SL Davis, TR Gunn. Lancet 1995;345:1353.

In infants under 6 months of age, air normally enters the trachea by the nose because the tongue fills the oral cavity, and the oral route is open only when the infant is making muscular efforts such as crying or gasping. The present recommendation for infant resuscitation is for the resuscitator's mouth to cover the mouth and nose of the baby. We set out to test whether this recommendation is feasible. We measured the dimensions of the faces of 28 babies aged between 2 and 4 months (the age when resuscitation is most often needed) and of the mouths of 25 of their mothers. Only 2 mothers would have been able to cover with their mouths the nose and closed mouth of 2 babies (not their own). The mannequins often used to teach adults to resuscitate infants are misleading because they present a wide open mouth, thus implying that that is the preferred route. We recommend that the nasal route of air entry be taught to parents for resuscitation of babies who have stopped breathing.

Physician Characteristics Associated with Decisions To Withdraw Life Support—NA. Christakis, DA Asch. Am J Public Health. 1995; 85(3):367.

OBJECTIVE: This study was undertaken to identify attributes of physicians associated with physicians' decisions to withdraw life support. METHODS: Of the 862 Pennsylvania internists surveyed and asked to make decisions in response to hypothetical vignettes and to report their actual experience with the withdrawal of life support, 485 (56%) responded. The data were analyzed with regression models. RESULTS: With other factors controlled, physicians were more willing to withdraw life support if they were young, practiced in a tertiary care setting, or spent more time in clinical practice; they were less willing if they were Catholic or Jewish. Physicians reported a higher frequency of actually withdrawing life support if they were young, had more contact with ICU patients, spent more time in clinical practice, or were specialists. Physicians with a greater willingness to withdraw were more likely to report having done so. CONCLUSIONS: Physicians' personal characteristics are associated with both their preferences and their practice in the withdrawal of life support, and a greater willingness to withdraw is associated with a higher frequency of withdrawal. The influence of physician characteristics demonstrates that patient preferences and clinical circumstances do not exclusively govern such ethical decisions. *See the related editorial: **Annotation: Physicians' Attitudes and Decision Making Regarding the Withdrawal of Life Support**—BW Levin. Am J Public Health. 1995;85(3): 306-307.*

Obstetrical Judgments of Viability and Perinatal Survival of Extremely Low Birthweight Infants—ML Reuss, HR Gordon. Am J Public Health 1995;85(3):362.

OBJECTIVES: The purpose of the study was to determine whether the obstetrical judgment of viability makes a difference to fetal and neonatal survival of extremely low birthweight infants (500-749 g). METHODS: We assessed the effect of the antenatal judgment of viability in a group of 66 infants born weighing from 500 to 749 g. These infants were alive at maternal hospital admission and were subsequently live-born or stillborn between January 1, 1984, and December 31, 1985. We related the antepartum assessment of viability and other factors recorded in the medical record to fetal survival and to postneonatal survival to hospital discharge. RESULTS: The obstetrical judgment of viability was strongly associated with outcome. After birthweight and gestational age were controlled, fetuses considered viable were 18 times more likely to survive (95% confidence interval = 2,175) than those considered nonviable. CONCLUSIONS: The effects of obstetrical practices on perinatal mortality must be taken into consideration in estimating the survival potential of very small fetuses and in evaluating the relationship between survival and disability. *See the related editorial: **Does Intensive Perinatal Care Improve the Outcome of Extreme Prematurity? Addressing the Methodologic Issues**— Am J Public Health 1995;85(3):300-302.*

Safety of Propellants—DJ Alexander. J Aerosol Med 1995;8(1, Suppl);S-29.

Chlorofluorocarbon (CFC) propellants used in metered dose inhalers (MDI) must be replaced under the terms of the Montreal Protocol. Following a review of the available data. HFA134a (1,1,1,2 tetrafluoroethane) was selected as a potential alternative propellant. However, because this data was insufficient to satisfy the stringent requirements for pharmaceuticals, additional toxicological assessments were performed. These included genotoxicology, animal inhalation studies, reproductive toxicology, local tolerability and safety pharmacology studies. A special grade of HFA134a, containing relatively high concentrations of all likely impurities was used for all pivotal studies. HFA134a was devoid of genotoxicity and had exceptional low acute toxicity. No toxicity was seen in rats or dogs exposed to concentrations of up to 5% or 12% respectively for up to one year. No fetotoxicity, effects on reproductive performance, peri- or post-natal development was demonstrated. HFA134a was devoid of oncogenic potential in rats and mice. There was no evidence of sensitization or local irritation to the skin or eyes. All species demonstrated high systemic HFA134a concentrations. An extensive toxicological evaluation, at very high multiples of the likely patient exposure, has indicated that HFA134a is a suitable alternative to CFC propellants for MDI's.

Clinical Evaluation of CFC-Free Metered Dose Inhalers—M Jenkins. J Aerosol Med 1995;8 (1, Suppl):S-41.

Current metered dose inhalers (MDIs) contain chlorofluorocarbon (CFC) propellants. A new propellant HFA134a, with no effect on ozone, may be a suitable alternative. Four asthma medications, salbutamol, salmeterol, fluticasone propionate (FP) and beclomethasone dipropionate (BDP), currently containing standard CFC propellants, were formulated with HFA134a for investigation. Single doses of salbutamol (200 μg) and salmeterol (50 μg, 100 μg) provided equivalent protection against bronchial provocation, after histamine and methacholine respectively, compared with the current preparation. A double-blind 4-week study comparing the two formulations of salbutamol, used as required in mild to moderate asthma, showed similar effects on morning peak expiratory flow rates (PEFR) and inhaler use. Salmeterol (50 μg) twice daily was compared with the current formulation in a 4-week trial. Improvement in morning PEFR was similar for both formulations. A double-blind study compared the two formulations of FP (250 μg) twice daily in moderate asthmatics previously taking 400-1,000 μg of inhaled corticosteroid daily. Morning PEFR improved in both groups. Safety and tolerability of the HFA134a product were similar to current formulations. The HFA134a formulations of salbutamol, salmeterol and FP provide equivalent ef-

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A Review of Cost Studies of Intensive Care Units: Problems with the Cost Concept—M Gyldmark. Crit Care Med 1995;23(5):964.

OBJECTIVE: To study methods for costing hospital services, specifically in relation to multi-unit studies of activity, case mix, severity of illness, outcome, and resource use in adult intensive care units (ICUs). DATA SOURCES: Twenty published cost studies of adult ICUs. The studies are all published in English and are both European and American. STUDY SELECTION: Cost studies of adult ICUs published in international journals (English language). DATA EXTRACTION: Literature survey, where the articles were obtained through MEDLINE and other database searches. DATA SYNTHESIS: Cost of intensive care therapy was compared across the 20 studies. However, as stressed in the article, to compare costs of intensive care therapy across units is not possible for a number of reasons. One of the reasons for this limitation is that the studies employed different approaches to costing and thereby introduced a methodologic bias. In addition, the costing methodology applied in the majority of the studies was wrongly specified in relation to the purpose and viewpoint of the studies. CONCLUSIONS: The methodologies for costing ICU therapy are flawed and fail to provide correct answers. In most studies, the study question is not adequately specified and the cost concept used in the studies is not tailored to the purposes of the study. Standardizing the cost model would lead to better, faster, and more reliable costing. This standardized cost model should not be rigid, but adaptable to different decision situations. A decision tree or taxonomy is proposed as a way toward better costing of ICU activity. *See the related editorial:* ***Economic Analysis of the Intensive Care Unit: A Dilemma****—Crit Care Med 1995;23(5):805.*

Simple Method To Measure Total Expiratory Time Constant Based on the Passive Expiratory Flow Volume Curve—JX Brunner, TP Laubscher, MJ Banner, G Iotti, A Braschi. Crit Care Med 1995;23(6):1117.

OBJECTIVE: In intubated, mechanically ventilated patients, inspiration is forced by externally applied positive pressure. In contrast, exhalation is passive and depends on the time constant of the total respiratory system. The expiratory time constant is thus an important determinant of mechanical ventilation. The aim of this study was to evaluate a simple method for measuring the expiratory time constant in ventilated subjects. DESIGN: Prospective study using a lung simulator and ten dogs. SETTING: University hospital. SUBJECTS: Commercially available lung simulator and ten greyhound dogs. INTERVENTIONS: Different expiratory time constants were set on the lung simulator. In the dogs, the endotracheal tube was clamped to increase airways resistance by 22.5 cm H_2O/(L/ sec) and the lungs were injured with hydrochloric acid to decrease total respiratory compliance by 16 mL/cm H_2O. This procedure resulted in a wide range of expiratory time constants. MEASUREMENTS AND MAIN RESULTS: Pneumotachography was used to measure flow and volume. The ratio of exhaled volume and peak flow was calculated from these signals, corrected for the limited exhalation time yielding the "calculated expiratory time constant," and compared with the actual expiratory time constant. The typical error was ± 0.19 sec for the lung simulator and ± 0.15 sec for the dogs. CONCLUSIONS: The volume and peak flow corrected for limited exhalation time is a good estimate of the total expiratory time constant in passive subjects and may be useful for the titration of mechanical ventilation.

Probability of Survival after Prolonged Extracorporeal Membrane Oxygenation in Pediatric Patients with Acute Respiratory Failure—TP Green, FW Moler, DM Goodman, for the Extracorporeal Life Support Organization. Crit Care Med 1995;23(6):1132.

OBJECTIVE: Extracorporeal membrane oxygenation (ECMO) has been used with increasing frequency for respiratory failure that is unresponsive to conventional therapy. We examined the relationship between duration of ECMO and outcome to understand whether prolonged ECMO (duration of the procedure for > 14 days) was more commonly associated with futile therapy or eventual recovery. DESIGN: A cohort study of all patients reported to the Pediatric ECMO Registry for Acute Respiratory Failure of the Extracorporeal Life Support Organization. SETTING: Tertiary hospitals (n = 83) capable of providing extracorporeal support for pediatric patients. PATIENTS: Children (n = 382) between the ages of 1 wk and 18 yrs of age with severe respiratory failure. INTERVENTIONS: Extracorporeal membrane oxygenation. MEASUREMENTS AND MAIN RESULTS: The death or live hospital discharge of ECMO-treated patients, together with the post-ECMO mechanical ventilation course, were examined as a function of duration of ECMO and of pre-ECMO respiratory status. The occurrence of complications and the causes of death were also noted. The criteria used to initiate ECMO, as well as the determination of the futility of further ECMO, were determined by local practice at individual centers. There were 382 patients treated with ECMO, of whom 184 (48%) survived. The proportional survival in the patients treated for the longest duration was similar to the overall group. The cause of death was given for 168 patients: 32 neurologic deaths; nine deaths due to ECMO complications; and 30 deaths due to nonpulmonary organ failure. There were 97 deaths due to elective ECMO termination; 80 of these deaths occurred after the determination of the futility of anticipating pulmonary recovery. The latter deaths occurred at widely varying durations of ECMO, with a median of 282 hrs. However, at that same duration, 47 eventual survivors (26% of all survivors) continued to receive ECMO. By discriminant analysis, the survival rate was independently related ($r^2 = 0.18; p < 0.0001$) to peak ventilator inspiratory pressure before ECMO and duration of intubation before ECMO, patient age, and the occurrence of several complications. CONCLUSIONS: While the survival rate in pediatric patients receiving ECMO appears related to the severity of lung disease and to the occurrence of ECMO complications, the survival rate in patients treated with ECMO courses of > 2 wks was similar to the survival rate of patients treated for shorter periods of time. ECMO was terminated in some patients for pulmonary futility at durations of ECMO associated with survival in substantial numbers of patients in whom ECMO was continued.

Noninvasive Monitoring of End-Tidal Carbon Dioxide Tension via Nasal Cannulas in Spontaneously Breathing Children with Profound Hypocarbia—JFK Flanagan, JS Garrett, A McDuffee, JD Tobias. Crit Care Med 1995;23(6):1140.

OBJECTIVE: To determine the correlation between end-tidal CO_2 and P_{aCO_2} measured via nasal cannulas in spontaneously breathing children with profound hypocarbia ($P_{aCO_2} < 30$ torr [< 4.0 kPa]). DESIGN: Prospective evaluation. SETTING Pediatric intensive care unit (ICU) in a tertiary care referral center. INTERVENTIONS: None. PATIENTS: Patients admitted to the ICU with a diagnosis of diabetic ketoacidosis in whom invasive arterial access was deemed necessary for clinical care. The patients were spontaneously breathing, without intubation. The study included nine patients, with an average age of 9.9 yrs (range 4 to 17) and weight of 38.7 kg (range 17 to 68). MEASUREMENTS AND MAIN RESULTS: End-tidal CO_2 was sampled from nasal cannulas by a sidestream aspirator and estimated by infrared spectroscopy. The correlation between arterial and end-tidal CO_2 was compared using linear regression analysis. A total of 65 arterial blood gases were obtained from the nine patients. The P_{aCO_2} was ≤ 30 torr (≤ 4.0 kPa) in 38 of the samples. The P_{aCO_2} to end-tidal CO_2 gradient was ≤ 4 torr (≤ 0.5 kPa) in 64 of 65 samples and 4.8 torr (0.6 kPa) in one sample. Linear regression analysis of arterial vs end-tidal CO_2 yielded a slope of 0.99, an r^2 value of 0.97, and a p value of 0.0001. CONCLUSIONS: End-tidal CO_2 measurement by infrared spectroscopy provides an accurate estimation of P_{aCO_2}, even during episodes of severe hypocarbia. Its use may limit the need for invasive monitoring and/or repeated arterial blood gas analyses.

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The Effect of Bronchopulmonary Dysplasia on Growth at School Age—LA Vrlenich, MEA Bozynski, Y Shyr, MA Schork, DW Roloff, MC McCormick. Pediatrics 1995;95(6):855.

OBJECTIVE: To determine the effect of bronchopulmonary dysplasia (BPD) on growth at school age. DESIGN: A prospective cohort study. METHODS: The sample included 406 children selected from a reconstructed cohort of infants of very low birthweight previously enrolled in a multisite, randomized, controlled clinical trial. The children were contacted at 8 to 10 years of age. Height, weight, and head circumference (HC) were measured. Possible confounders including sociodemographic data, and neonatal factors were also recorded. RESULTS: The children in the BPD group were significantly smaller in weight (z score, -0.50 ± 1.19 SD vs -0.06 ± 1.30 SD) and HC (z score, -1.41 ± 1.32 SD vs -0.63 ± 1.62 SD) than those without BPD. However, after controlling for confounders (using analysis of covariance), no significant differences were demonstrated between the two groups. Power analyses showed that a difference of at least 0.43 z-score units could have been detected. The previously documented associations between BPD and suspected confounders were reconfirmed. CONCLUSIONS: Significant differences were noted between children with and without BPD for weight and HC but not height. When possible confounders were taken into account, the differences were no longer appreciated. Thus, the previously reported poor growth in children with BPD may have been related to other factors and not necessarily to BPD.

Prolonged Episodes of Hypoxemia in Preterm Infants Undetectable by Cardiorespiratory Monitors—CF Poets, VA Stebbens, D Richard, DP Southall. Pediatrics 1995;95(6):860.

OBJECTIVE: To determine whether episodes of prolonged hypoxemia occur without prolonged apneic pauses (≥ 20 seconds) and without bradycardia (pulse rate, ≤ 100 beats per minute) in apparently well preterm infants. METHODS: Long-term recordings of arterial oxygen saturation as measured by pulse oximetry (S_{pO_2}), photoplethysmographic (pulse) waveforms from the oximeter, and breathing movements were performed in 96 preterm infants (median gestational age at birth, 34 weeks; range, 28 to 36 weeks) who were breathing room air. Recordings started at a median age of 4 days (range, 1 to 60 days). RESULTS: During a median duration of recording of 25 hours, 88 episodes in which S_{pO_2} fell to 80% or less and remained there for 20 seconds or longer were identified in 15 infants. The median duration of these prolonged desaturations was 27 seconds (range, 20 to 81 seconds). In 73 episodes (83%), S_{pO_2} continued to fall to 60% or less. Twenty-three desaturations were associated with prolonged apneic pauses and 54 with bradycardia; 19 of these were associated with both apnea and bradycardia. Thirty desaturations (34%; 10 infants) occurred without bradycardia and without prolonged apnea. CONCLUSIONS: These results indicate that a proportion of apparently well preterm infants exhibit episodes of severe prolonged hypoxemia unaccompanied by prolonged apneic pauses or bradycardia. Such episodes, therefore, would be difficult to detect if only breathing movements and heart rate are monitored. Indications for the use of oxygenation monitors in preterm infants should be reconsidered.

Prevention Of Atelectasis during General Anaesthesia—HU Rothen, B Sporre, G Engberg, G Wegenius, A Reber, G Hedenstierna. Lancet 1995;345:1387.

Atelectasis is an important cause of impaired gas exchange during general anaesthesia; it causes pulmonary shunting. We studied the effects of gas composition on the formation of atelectasis and on gas exchange during the induction of general anaesthesia. In 12 adult patients, the lungs were ventilated with 30% oxygen in nitrogen during anaesthesia induction, and in another 12, a conventional technique was used (100% oxygen during induction and 40% oxygen in nitrogen thereafter). Extent of atelectasis was estimated by computed tomography and the ventilation-perfusion relation ($\dot{V}_A/\dot{Q}$) by the multiple inert gas elimination technique. After anaesthesia induction, there was little atelectasis in the 30% oxygen group (mean 0.2 [SD 0.4] cm^2) and a significantly greater amount (4.2 [5.6] cm^2; $p < 0.001$) in the 100% oxygen group. Patients in the 30% oxygen group were observed for another 40 min. 6 continued to receive 30% oxygen (subgroup A) and 6 were ventilated with 100% oxygen (subgroup B). During this time, the amount of atelectasis increased to 1.6 (1.6) cm^2 in subgroup A and to 4.7 (4.5) cm^2 in subgroup B ($p = 0.047$ for difference between groups). In subgroup A, the shunt ($\dot{V}_A/\dot{Q} < 0.005$) increased from 1.6 (2.0)% of cardiac output to 3.2 (2.7)%, but the arterial oxygen tension did not change. In subgroup B, the shunt increased from 2.6 (5.2)% to 9.8 (5.7)% of cardiac output. These results suggest that the composition of inspired gas is important in atelectasis formation during general anaesthesia. Use of a lower oxygen concentration than is now standard practice might prevent the early formation of atelectasis.

Continuous versus Intermittent Nebulized Terbutaline: Plasma Levels and Effects—FW Moler, CE Johnson, C VanLaanen, JM Palmisano, SZ Nasr, O Akingbola. Am J Respir Crit Care Med 1995;151:602.

The purpose of this investigation was to compare continuous versus intermittent nebulization of a β-2-agonist, terbutaline, to determine whether differences exist in plasma concentrations or adverse cardiovascular effects of the drug with these two techniques for its administration. Sixteen children 6 to 16 years of age, admitted for acute asthma, were enrolled in this randomized double-blind clinical trial. Nebulization of 16 mg of terbutaline over an 8-h period was performed either continuously or intermittently, with a dose of 4 mg given over 20 min every 2 h. The peak plasma terbutaline concentration for the intermittent nebulization treatment (INT) group (5.1 ± 2.1 ng/mL) occurred 1 h after the fourth inhalation treatment and was similar to the peak concentration for the continuous nebulization treatment (CNT) group, which was reached at the end of the 8 h period (4.7 ± 2.3 ng/mL). The maximum heart rate increase for the INT group (19.6 ± 18.3 beats/min) occurred 1 h after the fourth dose and was similar to the peak observed in the CNT group (19.6 ± 19.2 beats/min), which occurred after 3 h. Similar increases in systolic and decreases in diastolic pressures were observed for the INT and CNT groups. No evidence of serious adverse myocardial complications was seen in either group, as evidenced by measurements of the MB fraction of creatine phosphokinase (CPK-MB) and Holter-monitor recordings. Continuous nebulization of the terbutaline produces similar plasma concentrations and cardiovascular physiologic responses as intermittent nebulization. These findings suggest that the improved therapeutic efficacy of frequent or continuous, β-2-agonist administration is not secondary to a greater systemic drug concentration achieved with this technique but rather to more optimal direct local pulmonary effects.

Prospective Study of Hospitalization for Asthma: A Preliminary Risk Factor Model—D Li, D German, S Lulla, RG Thomas, SR Wilson. Am J Respir Crit Care Med 1995;151:647.

We conducted an exploratory analysis of several prospectively obtained objective measures of disease activity to derive a predictive model of hospitalization for asthma among 310 adults, ages 18 to 50 years, with moderate to severe asthma. Baseline characteristics associated with increased risk of hospitalization in the succeeding year include (1) prior year hospitalization, (2) moderate or severe respiratory impairment, (3) a medication regimen consistent with severe asthma, (4) a history of significant systemic steroid use, (5) maximum overnight PEF variability > 40%, and (6) mean evening PEF < 60% of predicted (relative risk = 6.5, 6.9, 8.1, 3.7, 3.0, and 3.2, respectively). Recursive partitioning analysis, depicted as a "classification tree," provided a more sensitive (94%) and specific (68%) multivariate description of the data set than either logistic regression (87 and 48%, respectively) or a simple additive risk model (46 and 93%, respectively). Patients with very high (> 50%), moderately elevated (10 to 15%), and very low (< 5%) risk of hospitalization were identified on the basis of particular combinations of prior hospitalization history, level of respiratory impairment, and medication regimen. Overnight variability and mean

evening PEF measured at home over a 2-wk period proved less informative for risk stratification than respiratory impairment determined once at baseline by office spirometry. The findings warrant replication and extension in other populations with the goal of developing decision rules for risk stratification and effective interventions for risk reduction.

Sleep Apnoea and Nocturnal Angina—KA Franklin, JB Nilsson, C Sahlin, U Näslund. Lancet 1995;345:1085.

Hypoxaemia occurs with sleep apnoea and might induce nocturnal angina. Sleep apnoea was found in 9 of 10 patients with nocturnal angina pectoris. Nocturnal angina diminished during treatment of sleep apnoea by continuous positive airway-pressure, and the number of nocturnal myocardial ischaemic events measured by computerised vector-cardiography was reduced.

The Familial Aggregation of Obstructive Sleep Apnea—S Redline, PV Tishler, TD Tosteson, J Williamson, K Kump, I Browner, V Ferrette, P Krejci. Am J Respir Crit Care Med 1995; 151:682.

An inherited basis for sleep-disordered breathing (SDB) has been suggested by reports of families with multiple affected members and by a previous study of the familial aggregation of symptoms of SDB. In this study, we quantify and characterize the aggregation of SDB and assess the degree to which familial similarities may be independent of obesity. This was a genetic-epidemiologic study that assessed the distribution of SDB in families identified through a proband with diagnosed sleep apnea and among families in the same community with no relative with known sleep apnea. SDB was assessed with overnight in-home monitoring of airflow, oxygen saturation, chest wall impedance, heart rate, and body movement. Standardized questionnaires were used to assess symptoms, and weight, height, and neck circumference were measured directly. Intergenerational and intragenerational correlation coefficients and pairwise odds ratios (ORs) were calculated with adjustment for proband sampling. In toto, 561 members of 91 families were studied: (1) 47 subjects with laboratory-confirmed SDB (index probands), (2) 44 community control subjects, and (3) the spouses and relatives of 1 and 2. Of all 91 families, 32 (35%) had two or more members with SDB, 30 (33%) had one affected member, and 29 had no affected members. SDB was more prevalent in the relatives of index probands (21%) than among neighborhood control subjects (12%) ($p = 0.02$). After adjusting for age, sex, race, and obesity, the odds of SDB, defined on the basis of age-specific threshold values for the respiratory disturbance index (RDI), was 1.3 greater in subjects with one affected relative, and 2.3 greater in subjects with three affected members when compared with subjects without affected family members. Intergenerational and intragenerational coefficients, describing the similarities in RDI levels among family members, were each 0.21 ($p < 0.005$), and they were not reduced significantly with adjustment for obesity. These results suggest that SDB significantly aggregates within families and that risk increases progressively with increasing numbers of affected relatives. The familial aggregation of SDB is not explained entirely by familial similarities in body mass index (BMI) or neck circumference, suggesting the importance of other familial factors in increasing susceptibility to the disorder.

Assessment of the Role of Inheritance in Sleep Apnea Syndrome—G Pillar, P Lavie. Am J Respir Crit Care Med 1995;151:688.

Several reports have suggested a genetic importance in the pathogenesis of the sleep apnea syndrome (SAS). In this study, all adult (> 16 yr of age) offspring of 45 randomly selected parents with previously diagnosed SAS were asked to undergo a whole-night polysomnographic study. One hundred and five of 120 candidates participated in the study (66 M:39 F), with a high rate of compliance. Forty-seven percent of the offspring (36 males and 13 females; mean age, 32 years) were found to have SAS. These results appear considerably higher ($p < 0.001$) than the common estimation of the prevalence of SAS in the population (4%). Another 21.9% of the offspring were "simple snorers" (17 males and 6 females; mean age, = 26 years). Thirty-one percent were unaffected (13 males, 20 females; mean age, 29 years). Only 16% of males over 35 years of age were unaffected. In the single family studied in which both parents were affected, all three of their children (sons) had SAS: two grandsons older than 16 years were simple snorers. Considering the well-established prevalence of SAS in the general population (1 to 4%), these results may suggest that SAS is an inherited syndrome.

Effect of Synchronized, Systolic, Lower Body, Positive Pressure on Hemodynamics in Human Septic Shock: A Pilot Study—JP Gunter, BP deBoisblanc, BS Rust, WD Johnson, WR Summer. Am J Respir Crit Care Med 1995;151:719.

The pathophysiologic disturbance observed in volume-resuscitated patients with septic shock is primarily that of hyperdynamic circulation with a markedly reduced systemic vascular resistance. We hypothesized that external, mechanically applied, phasic lower body positive pressure could increase systemic vascular resistance and, thus, blood pressure in patients with refractory septic shock. A total of nine studies were performed on seven patients with septic shock refractory to volume resuscitation and vasopressors. All pre-existing therapies were continued unaltered during the study period. Phasic lower body positive pressure was produced by rapid synchronized inflation of pneumatic fabric cuffs fitted around each lower extremity. The cuffs were inflated for 200 ms to a pressure of 150 mm Hg, and the timing of inflation was adjusted to coincide with the peak systolic arterial pressure. Hemodynamic measurements were obtained at baseline and after 15 min of phasic lower body positive pressure. This off-on cycle was repeated twice for each study. Phasic lower body positive pressure increased mean arterial pressure by 12% and cardiac index by 14% ($p = 0.01$) over baseline ($p \leq 0.001$). Heart rate, central venous pressure, pulmonary capillary wedge pressure, arterial pH, arterial P_{O_2}, and mixed-venous P_{O_2} were unchanged. Synchronized external systolic compression of the lower extremities increased mean arterial pressure and cardiac output in seven patients with refractory septic shock. This hemodynamic improvement was independent of changes in calculated systemic vascular resistance.

Chest Physical Therapy Management of Patients with Cystic Fibrosis: A Meta-Analysis—J Thomas, DJ Cook, D Brooks. Am J Respir Crit Care Med 1995;151:846.

The purpose of this overview is to quantitatively assess the conflicting body of literature concerning the efficacy of physical therapy modalities for clearing bronchial secretions in the treatment of patients with cystic fibrosis (CF). The modalities examined included positive expiratory pressure (PEP) mask, forced expiratory technique (FET), exercise (EX), autogenic drainage (AD), and standard physical therapy (STD), consisting of postural drainage, percussion, and vibration. Computerized searches of the MEDLINE and Cumulative Index for Nursing and Allied Health databases were performed for the years from 1966 to 1993. The authors of relevant papers were contacted for unpublished information. Studies were considered relevant if they met the following criteria: randomized trials in patients with a definite diagnosis of CF; an intervention of any combination of PEP, FET, STD, AD, or EX; and an outcome of FEV_1, sputum weight, or sputum clearance. A review of 456 citations yielded 65 potentially relevant trials and 8 review articles; of these, 35 met the inclusion criteria and were incorporated into the overview. These studies evaluated different combinations of physical therapy modalities; therefore, we performed seven separate meta-analyses comparing the independent techniques using the pooled effect size technique. Standard physical therapy resulted in a significantly greater sputum expectoration than no treatment (effect size of 0.61 SD units, $p < 0.0001$). The combination of standard therapy with EX was associated with a statistically significant increase in FEV_1 over STD alone (effect size of 0.48 SD units, $p = 0.04$). No other differences between physical therapy modalities were found.

Broadening Our Outlook—
Oxygen Therapy in the People's Republic of China

Technology has made the world a much smaller place, and we should indeed consider ourselves a part of the global health-care system. Western medical technology is certainly spreading around the world, carrying with it the excitement of advances as well as the economic difficulties with which we in the United States are learning to live.

As part of the global health-care system, the AARC has an active International Council including members from the Pacific Rim, Italy, Mexico, and Central and South America.[1] A topic of particular interest to Council members and other AARC members is the application of technology from the United States in different economic, environmental, and governmental climates.

In this issue of the Journal we get a glimpse of how medical technology affects the use of home oxygen therapy in the People's Republic of China (PRC).[2] Dr Lin Cai Yuan and colleagues report their experience with pulse-dose oxygen therapy versus continuous oxygen therapy in the home. The authors have done an excellent study that is practical and applicable, and they deserve to be congratulated. There are, however, some interesting contrasts between the practice of home oxygen therapy in the United States and in China, which deserve mention.

Quick perusal of the paper brings the first clue—cylinders are always used in China because oxygen concentrators and liquid systems are unavailable. Of course, it is important to remember that the PRC remains a Communist state, which confuses the issue of reimbursement. Whereas in America it may *seem* that most home oxygen therapy is paid for by the Federal Government, in the PRC that is certainly the case. So, whereas we might be concerned with reimbursement related to home oxygen therapy and the convenience afforded by the reduced oxygen use that the pulse-dose devices provide, Dr Yuan and colleagues face other issues. If the use of pulse-dose oxygen delivery increases the length of cylinder life by 300% as Dr Yuan demonstrates, then fewer cylinders per patient are used over time, allowing more patients to receive oxygen therapy for a given number of available cylinders. Thus, the pulse-dose device, which in the United States is used to save a fairly inexpensive commodity (oxygen) and to extend the time that a patient can be away from his primary oxygen source, in the PRC provides a unique and valuable benefit to Dr Yuan's patients. In the PRC, the same device provides an advantage to patients that may previously have had little meaning for those caring for patients in the United States.

I want to extend my personal congratulations to Dr Yuan and his colleagues for a work well done. I also look forward to a more international character of RESPIRATORY CARE and more opportunities to ponder the unique problems faced by our colleagues in the global respiratory care community.

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Clinical Evaluation of Pulse-Dose and Continuous-Flow Oxygen Delivery

Lin Cai Yuan MD, Zeng Jun MD, and Lin Pei Min MD

INTRODUCTION: Several methodologies have been introduced to reduce oxygen (O_2) usage during home O_2 therapy. Pulse-dose O_2 therapy has been reported to reduce O_2 usage and costs. PURPOSE: Our purpose was to compare the clinical effectiveness and cost of pulse-dose O_2 therapy to continuous-flow O_2 therapy via nasal cannula in patients with chronic obstructive pulmonary disease (COPD), who were living at home. METHODS: We analyzed arterial blood samples drawn from 20 patients with hypoxemia on room air (mean P_{aO_2} 52 torr) while they were using continuous-low O_2 at 2 L/min and while they were using pulse-dose O_2 at a dose of 33 mL/pulse. In addition, total O_2 usage was determined by monitoring cylinder usage while patients used each delivery method at home. RESULTS: We found no difference in mean P_{aO_2} (90 ± SD 13 vs 91 ± SD 11 torr) or P_{aCO_2} (44 ± SD 8 vs 42 ± SD 6 torr) between the two delivery methods during home use. The cylinders lasted nearly three times longer with pulse-dose usage than with continuous-flow O_2 (86 ± 2 vs 30 ± 1 h). Patients did not express a preference for one device over the other. CONCLUSION: Pulse-dose O_2 therapy provides oxygenation equivalent to continuous-flow O_2 while using only one third the amount of O_2. This may reduce O_2 cost and delivery costs and provide therapy for more patients when supplies are limited. (Respir Care 1995;40(8): 811-814).

Introduction

The safety and efficacy of long-term home oxygen (O_2) therapy in patients with chronic obstructive pulmonary disease (COPD) is well documented.[1,2] However, the cost of home O_2 therapy remains a concern.

Recent techniques to decrease O_2 therapy costs include the use of reservoir devices, transtracheal O_2, and demand delivery devices.[3-16] Each of these techniques seeks to reduce O_2 costs by allowing a lower or intermittent flow while maximizing efficiency by delivering O_2 as early as possible in the inspiratory phase.

The purpose of this study was to compare the clinical effectiveness and cost of O_2 therapy delivered by a pulse-dose device to continuous low-flow O_2 delivery, in the home of patients with hypoxemia in the Peoples Republic of China (PRC).

Methods

Twenty patients currently receiving home O_2 therapy were studied. The study population consisted of 14 men and 6 women with a mean (SD) age of 58 (± 11 years, range 31-83). Prior to the initiation of O_2 therapy, all patients had arterial blood drawn and analyzed while they were breathing room air. The mean (SD) arterial O_2 tension (P_{aO_2}) was 52 (± 10 torr). Four patients also had hypercarbia with mean (SD) arterial carbon dioxide tension (P_{aCO_2}) of 51 (5) torr (range 47-57 torr). Table 1 lists the sex, age, diagnosis, and room-air P_{aO_2} of patients in the study.

Patients were initially placed on continuous-flow O_2 via a nasal cannula at 2 L/min. After a period of stabilization, they were asked to sit quietly for 1 hour. At the end of this 1-hour period, blood was obtained from the radial artery using standard aseptic technique. Patients were then placed on pulse-dose O_2 therapy using a Pulsair OMS50 device (Devilbiss,

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Table 1. Clinical Data on 20 Patients before Oxygen Therapy Began

Case	Sex	Age	Diagnosis	P_{aO_2} torr
1	M	56	Chronic bronchitis	46
2	F	59	Chronic bronchitis, obstructive emphysema	58
3	F	62	Chronic bronchitis	42
4	M	48	Chronic bronchitis	41
5	M	56	Chronic bronchitis	55
6	M	78	Obstructive emphysema, cor pulmonale	73
7	M	48	Bronchial asthma	54
8	M	76	Chronic bronchitis, obstructive emphysema, cor pulmonale	40
9	F	63	Chronic bronchitis	43
10	M	67	Chronic bronchitis, obstructive emphysema, cor pulmonale	52
11	M	58	Chronic bronchitis	68
12	F	31	Bronchiectasis	45
13	F	59	Chronic bronchitis	42
14	M	47	Chronic bronchitis	66
15	M	62	Chronic bronchitis, obstructive emphysema, cor pulmonale	52
16	M	68	Chronic bronchitis, obstructive emphysema, cor pulmonale	57
17	F	59	Chronic bronchitis	42
18	M	66	Coronary heart disease	51
19	M	75	Coronary heart disease	44
20	M	72	Coronary heart disease	72

Somerset PA) with flow set to deliver a pulse of O_2 for 0.2 seconds at a flow of 10 L/min. After another period of stabilization, patients were asked to sit quietly for 1 hour. A second blood sample was then obtained from a radial artery and analyzed.

The O_2 use with each technique was assessed in 4 patients. Each patient was provided with 4 full O_2 cylinders (volume 6.2 m^3, pressure 130 kg/cm^2). In sequence the patients used continuous or pulse-dose O_2 therapy. The time at which O_2 therapy was initiated and the time at which each cylinder became empty was recorded. This was accomplished while patients went about their normal daily home routines. These data were used to determine length of cylinder life and costs.

A cylinder of O_2 in the PRC costs approximately 33 yuan, or about $3.84 U.S. (The current United States exchange rate of yuan for dollars is 8.6 yuan per dollar.)

Data were compared using a paired t-test and simple regression analysis.

Results

There was no statistically significant difference in P_{aO_2} between the groups. During continuous-flow O_2 the mean (SD) P_{aO_2} was 90 (± 13) torr and 91 (± 11) torr during pulse-dose delivery. Comparison of P_{aO_2} during continuous flow to P_{aO_2} during pulse-dose delivery showed an excellent correlation ($r^2 = 89$). In 7 patients, P_{aO_2} was higher using continuous-flow O_2, in 11 patients P_{aO_2} was higher using pulse-dose O_2 therapy, and in 2 patients P_{aO_2} was the same (Fig. 1).

There was also no difference in P_{aCO_2} between groups. Patients had a mean (SD) P_{aCO_2} of 44 (± 8) torr during continuous-flow O_2 therapy and a mean (SD) P_{aCO_2} of 42 (± 6) torr during pulse-dose O_2 therapy. Figure 2 compares P_{aO_2} and P_{aCO_2} in the two modes. Mean (SD) cylinder life during continuous-flow O_2 was 30 (± 1) h and 86 (± 2) h during pulse-dose O_2 therapy. Based on cylinder size and set flow, expected cylinder life was 29 hours. The difference in duration of cylinder life between the two devices was statistically significant ($p < 0.0001$).

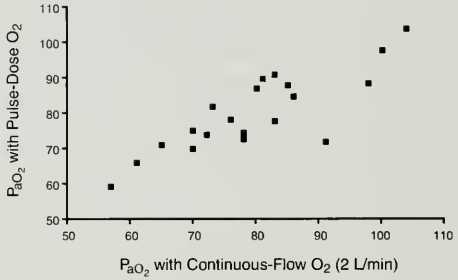

Fig. 1. Correlation between P_{aO_2} of patients on continuous O_2 therapy and P_{aO_2} of those on pulse-dose O_2 therapy.

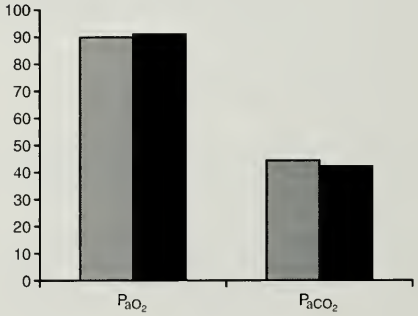

Fig. 2. Mean values for P_{aO_2} and P_{aCO_2} while patients were receiving oxygen therapy via each delivery method. ▨ designates continuous-flow therapy; ■ represents pulse dose.

Discussion

This study confirms the findings of several previous works[7-13]—that is, pulse-dose O_2 is capable of providing equivalent oxygenation to those patients using continuous-flow O_2 in the home. Our results also confirm that less O_2 is used and

demonstrate the cost-savings associated with pulse-dose O_2 delivery. Cylinders lasted three times longer with the pulse-dose device than with continuous flow. This may have importance beyond cost alone in situations in which the total oxygen supply is limited.

The impetus behind the development of pulse-dose O_2 delivery devices was cost.[14] Early providers realized the wastefulness of continuous-flow O_2 delivery, which is exacerbated by the breathing pattern of the COPD patient who typically has a prolonged expiratory phase and an inspiratory-to-expiratory-time ratio of 1:3 or even 1:4. In this instance, the O_2 flowing during the expiratory phase (65% or more of the total respiratory-cycle time) is lost to the atmosphere.

Other methods to reduce O_2 waste include conserving devices (eg, reservoir cannulas) and transtracheal O_2 (TTO) delivery. The pulse-dose O_2 therapy device allows oxygenation comparable to continuous-flow O_2 without the obtrusive appearance of a reservoir device or the surgical procedure of TTO. In our experience, the pulse-dose device allows for the maximum efficiency and cost-savings of O_2-conserving technologies.

Others have demonstrated the cost-savings of pulse-dose oxygen therapy. Mecikalski and Shigeoka found that O_2 use was reduced by a mean of 28% compared to continuous flow in a group of stable COPD patients.[10] Tremper et al[15] found that O_2 use was reduced by 17% in a group of 8 COPD patients at home. Several papers on pulse-dose O_2 therapy[10,11,13,15] report short-term results obtained in the laboratory with no follow-up on patients at home ie, they establish only efficacy, limiting the extrapolation of the results. Our study was performed in the home in an effort to detect actual improvements in O_2 conservation ie, effectiveness.

The pulse-dose device operates by sensing patient inspiration and delivering a 'burst' of O_2 early in the inspiratory phase. The device setting for flow is equivalent to 10 L/min, and the pulse period is 0.2 seconds. This provides an O_2 volume of 33 mL/pulse, which approximates a continuous flow of O_2 at 2 L/min. Another advantage of the pulse-dose device is the rate-dependent delivery of O_2. As the patient's respiratory rate decreases, O_2 usage is further reduced.

In several studies, the effectiveness of pulse-dose oxygen therapy during exercise has been questioned.[8,11,16] McDonnell et al[11] and Tiep et al[16] have shown decreased oxygenation associated with use of a pulse-dose delivery device during exercise. Hoffman has suggested that patients using a pulse-dose delivery device have separate prescriptions, one for rest and one for exercise.[14] In our series, no patient complained of dyspnea while using the device, and no periods of arterial O_2 desaturation were recorded. We did not test our patients during exercise.

Another issue related to pulse-dose O_2 therapy is the change in sensation of flow experienced by the patient. Hoffman has suggested some patients might find the burst of oxygen early in the inspiratory phase uncomfortable, which might result in lower acceptance of the device.[14] This burst might cause irritation of the nasal cavity and interrupt patient rest. Our patients did not specify a preference for either type of delivery method, and no patient complained about the sensation created by the pulse-dose device.

A unique facet of our study is the environment in which the study was performed. In the PRC, all patients on home O_2 therapy use cylinders of gas; liquid systems and concentrators are not available. During use of pulse-dose O_2 therapy, cylinder life was extended nearly threefold. Based on cost (one cylinder is 33 yuan), pulse-dose O_2 therapy results in a cost of 8.8 yuan per day vs 26.4 yuan per day for continuous-flow O_2. More importantly, in a country as large as the PRC under a universal health-care system, the reduction in O_2 use reduces the number of cylinder deliveries further reducing costs. In addition, because costs are borne by the government, the reduction in cylinder usage may allow more patients to be treated. The initial cost of the pulse-dose device appears to be made up for in O_2 and service cost reductions.

In summary, our results suggest that pulse-dose oxygen delivery can maintain equivalent oxygenation to continuous-flow oxygen at lower costs without changes in patient acceptance in a group of COPD patients in the home. We believe that in our population pulse-dose therapy has significant cost and clinical advantages over continuous-flow oxygen administration.

ACKNOWLEDGMENT

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FACE TO FACE WITH CHANGE

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Responses to Inhaled Bronchodilator in Patients with Acute Airflow Obstruction

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BACKGROUND: Subjective and physiologic responses to inhaled bronchodilator (BD) therapy in patients with obstructive airway disease are variable. Our objectives were (1) to compare changes in breathlessness and lung function based on randomization to either nebulized albuterol or normal saline; (2) to examine the stability of these responses in patients who received albuterol therapy on consecutive days. METHODS: Thirty-nine patients with obstructive airways disease who experienced an acute exacerbation and required hospitalization for therapy were studied before and after inhaled bronchodilator (BD) therapy to evaluate the responses in breathlessness and lung function. On Day 1, outcomes were measured before and after inhaled BD therapy. On Day 2, patients were randomized into a single-blind parallel-design study to receive either inhaled normal saline (placebo) or inhaled albuterol. The same outcomes were measured before and after the two different treatments. Main outcomes were ratings of breathlessness provided by the patient on the 0 to 10 category scale and spirometry—forced vital capacity (FVC) and volume exhaled in the first second of FVC (FEV_1). RESULTS: Two patients were excluded. Mean (SD) age of the 37 patients was 60 ± 18 years. Nineteen patients had chronic obstructive pulmonary disease, 15 had asthma, and 3 had cystic fibrosis. On Day 1, inhaled albuterol caused significant increases in both FVC and FEV_1 and a significant reduction in the perception of breathlessness. On Day 2, there were no significant changes in the outcome variables with inhaled normal saline, whereas inhaled albuterol produced bronchodilation and a reduction in the perception of breathlessness. There was no significant correlation ($r_s = 0.26$, $p = 0.12$) between the changes in FEV_1 and the changes in ratings of breathlessness following treatment with inhaled BD. Most patients (62%) hospitalized for an exacerbation of obstructive airway disease reported some relief of breathlessness with inhaled albuterol. CONCLUSIONS: Because no significant relationship between improvement in spirometry and reduction in breathlessness was evident, it may be important to assess the patient's level of breathlessness along with physiologic variables to gain a more comprehensive assessment of the response to inhaled BD therapy. [Respir Care 1995;40(8):815-819]

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The authors have no financial interests in any of the products mentioned in the paper or in competing products. The study was supported in part by a research grant from Schering-Plough Corp, Kenilworth, New Jersey.

Introduction

Inhaled albuterol, a β-2 adrenergic agonist, is recommended to dilate constricted airways in the treatment of acute and chronic airflow obstruction in patients with asthma and chronic obstructive pulmonary disease (COPD).[1,2] Bronchodilation should lead to reduced respiratory symptoms, particularly the patient's perception of breathlessness. Turner and colleagues[3] have shown

that metaproterenol, a β-2 agonist, improved lung function and relieved breathlessness in patients with asthma or COPD who developed acute airway obstruction and sought emergency care. Wolkove et al[4] showed similar overall benefits with albuterol in stable outpatients with obstructive lung disease, but reported that the change in FEV_1 (volume exhaled in the first second of a forced vital capacity [FVC]) following inhaled BD did not correlate with the change in breathlessness ($r = 0.05$). However, neither of these studies included a placebo group to compare with the inhaled BD group. Furthermore, we have heard the anecdotal descriptions of patients who, at times, report marked relief of dyspnea with inhaled BD but demonstrate little if any improvement in lung function.

The major purpose of this study was to evaluate breathlessness after inhaled BD therapy in hospitalized patients with obstructive airways disease (asthma, COPD, and cystic fibrosis). The hypothesis of the investigation was that patients would experience reduced breathlessness following inhaled BD but would report no change with placebo therapy. Based on the data by Wolkove et al[4] as well as our clinical observations, we proposed as a secondary hypothesis that changes in breathlessness would not significantly correlate with changes in spirometry. Specific objectives were (1) to compare responses of breathlessness and spirometry in patients randomized to receive either nebulized BD or normal saline and (2) to examine stability of subjective and objective responses in patients who received BD therapy on consecutive days.

Methods

Patients admitted to the Pulmonary Service at Mary Hitchcock Memorial Hospital for an exacerbation of their underlying obstructive airways disease were recruited to participate in the study. Sequential patients were considered and enrolled based on the availability of one of the authors (JL) to collect data on each subject for two successive days. Inclusion criteria were previous diagnosis of asthma, COPD, or cystic fibrosis based on the patient's outpatient medical record; acute deterioration leading to an increase in respiratory symptoms; a decision by an attending physician to hospitalize the patient for treatment; and an $FEV_1/FVC < 0.7$ at initial testing. Exclusion criteria included an unstable cardiovascular condition; inability to perform spirometry; and inability to understand and provide ratings of breathlessness. In order to detect a 1-unit difference in the change of breathlessness ratings (post-BD minus pre-BD values), given the change in the placebo group is 0, a sample size of 17 patients is required for each group ($1-\beta = 0.80$, α 0.05).

The study involved two consecutive days of testing. Day 1 included baseline measures of ratings of breathlessness, FVC and FEV_1 measurements, oxyhemoglobin saturation using pulse oximetry (S_{pO_2}), and heart rate (HR). On Day 2, subjects were randomized in a single-blind parallel-design study to receive either inhaled normal saline (placebo) or inhaled BD. The same outcome variables were measured before and after the two different therapies.

Patients entered the investigational protocol on the day of admission to the hospital (Day 1); diagnostic testing and therapy was instituted by the house staff under the supervision of the attending pulmonologist. Inhaled BD was prescribed via a nebulizer as initial therapy in addition to other medications (eg, intravenous corticosteroids, inhaled anticholinergic therapy, oral theophylline, and/or antibiotics). One of the authors (JL) was notified and then interviewed each patient within 6 hours of hospitalization to describe the study and testing procedure. All subjects who were interviewed agreed to participate in the study and provided written consent. The protocol had been approved by the Committee for the Protection of Human Subjects.

Initial testing was performed to coincide with the next scheduled administration of nebulized albuterol. Subjects were shown the 0-10 category-ratio (CR-10) scale developed by Borg[5] and were asked to read the following instructions:

> This is a scale for rating breathlessness (difficult or labored breathing). The number 0 represents no breathlessness. The number 10 represents the strongest or greatest breathlessness that you have ever experienced. Before receiving therapy you will be asked to select a number from the scale that represents your perceived level of breathlessness at that moment. After therapy has been administered you will be asked to repeat the above procedure.

The patient was asked whether he/she had any questions and was then instructed to select a number on the CR-10 scale.

Next, S_{pO_2} and HR were measured using a pulse oximeter (Nonin Medical Incorporated, Model 8500; Minneapolis MN). Spirometry was performed by each subject in a seated position according to the guidelines of the American Thoracic Society.[6] Three to five FVC maneuvers were obtained using a portable spirometer (Spirometrics Incorporated, Model 2500; Auburn ME). Predicted normal values were taken from Crapo et al.[7] Nebulized albuterol [2.5 mg (0.5 mL) in 2.5 mL normal saline] was given according to the previously written medical orders. Fifteen minutes after completion of nebulized BD therapy, ratings of breathlessness, S_{pO_2}, HR, and spirometry were measured in sequential order.

Testing on Day 2 was coordinated to occur 24 hours after Day-1 testing. Baseline values for breathlessness, S_{pO_2}, HR, and spirometry were obtained. Using a table of random numbers, patients were randomized to receive either nebulized albuterol or nebulized normal saline. Posttreatment outcome measures were obtained 15 minutes later. For subjects who received normal saline, nebulized BD was then administered as part of their medical therapy.

Baseline data were compared using an unpaired t-test, as were data from initial testing on Day 1 and the absolute change (post-BD minus pre-BD values) on the variables on Day 2, between groups. Pre- and post-BD values and absolute change

within each group on Days 1 and 2 were tested using a paired t-test. Because we were interested primarily in differences in the ratings of dyspnea on the CR-10 scale, the data most closely approximated a continuous measure. Therefore, mean values and t-tests were considered appropriate. Spearman's rank-order correlation coefficient was calculated to examine the relationship between the absolute changes in breathlessness and lung function with albuterol on Day 1. Differences were considered to be statistically significant only for $p < 0.05$.

Results

A total of 39 patients were recruited for the study and agreed to participate. Complete data are available for 37 subjects. Two individuals were excluded; one could not provide a reproducible effort for spirometry at initial testing, and the other person had difficulty understanding and using the CR-10 scale.

Characteristics of the entire sample as well as the albuterol and placebo groups are listed in Table 1. The values for FEV_1 indicate that, as a group, the patients had severe airflow obstruction at the time of hospitalization. No differences between the 2 groups at baseline were statistically significant for any of the variables (independent t-test, $p \geq 0.05$).

Pre-BD and post-BD values for the five outcome variables for each subgroup are given in Table 2. On Day 1 nebulized BD caused significant increases in FEV_1 and FVC, a significant reduction in ratings of breathlessness, and minimal changes in HR and S_{pO_2} in the 2 groups. On average, FEV_1 improved by 9.3% and 10.6% with nebulized BD in the placebo and BD groups, respectively.

Baseline values on Day 2 showed modest improvement in lung function (+100 mL and +90 mL in FEV_1 in placebo and BD groups, respectively) and modest reduction in ratings of breathlessness (–0.4 and –0.7 units on the CR-10 scale in placebo and BD groups, respectively) compared with baseline values taken on Day 1. On Day 2, there were no significant changes in any of the outcome variables with the placebo group, whereas inhaled BD produced significant improvements in spirometry, S_{pO_2}, and ratings of breathlessness (BD group). None of the absolute changes (post-BD minus pre-BD values) for any of the variables between Days 1 and 2 in the BD group were statistically significantly different.

None of the changes in FEV_1 or ratings of breathlessness with inhaled BD on Day 1 for the entire group were signif-

Table 1. Patient Characteristics, Medications, Baseline Spirometry, and Ratings of Breathlessness.

Characteristic	All Patients n = 37	Placebo n = 19	Bronchodilator n = 18
Age (years)	60.1 (18.8)	60.5 (19.6)	59.7 (18.7)
Gender			
Men	15	7	8
Women	22	12	10
Obstructive airway disease			
Asthma	15	9	6
CF	3	2	1
COPD	19	8	11
Medications			
β-2 agonists	33	17	16
Anticholinergics	18	9	9
Theophylline	21	9	12
Corticosteroids	30	13	17
Baseline spirometry			
FEV_1,% predicted	34.8 (15.2)	34.4 (14.4)	35.1 (16.1)
FVC, % predicted	63.6 (17.0)	65.1 (17.9)	62.1 (16.1)
Rating of breathlessness	3.2 (1.2)	2.9 (1.3)	3.4 (1.7)

Values are mean (SD) and counts; n = number of subjects; CF = cystic fibrosis, COPD = chronic obstructive pulmonary disease.
Comparisons of placebo to bronchodilator were not statistically significant (independent t-tests, $p \geq 0.05$).

Table 2. Comparison of Mean (SD) Before- and After-Bronchodilator (BD) Values for Ratings of Breathlessness, Spirometry, and Oxyhemoglobin Saturation.

	Placebo n = 19				Bronchodilator n = 18			
	Day 1		Day 2		Day 1		Day 2	
	Before-BD	After-BD	Before-BD	After-BD	Before-BD	After-BD	Before-BD	After-BD
Variable								
Ratings of breathlessness	3.0 (1.3)	2.4 (1.3)*	2.5 (1.7)	2.4 (1.3)	3.4 (1.7)	2.5 (1.7)*	2.7 (1.3)	2.0 (1.3)*
FEV_1 (L)	0.86 (0.35)	0.94 (0.31)*	0.96 (0.39)	0.98 (0.39)	0.96 (0.47)	1.08 (0.55)*	1.05 (0.51)	1.15 (0.59)*
FVC (L)	2.15 (0.65)	2.37 (0.65)*	2.30 (0.65)	2.39 (0.74)	2.13 (0.68)	2.36 (0.81)*	2.27 (0.64)	2.49 (0.72)*
Heart rate (beats/min)	94.5 (16.1)	98.3 (15.3)*	99.2 (18.3)	96.1 (17.0)	98.8 (14.4)	101.1 (16.5)	98.1 (11.4)	100.7 (10.6)
S_{pO_2} (%)	92.6 (3.1)	92.7 (3.1)	91.6 (4.4)	91.9 (4.4)	91.8 (3.0)	92.4 (3.0)	90.8 (3.8)	92.3 (3.0)*

* paired t-test comparing before-BD and after-BD values, $p < 0.05$
FEV_1 = volume exhaled in the first second of a forced vital capacity—FVC; S_{pO_2} = saturation of oxygen measured by pulse oximetry.

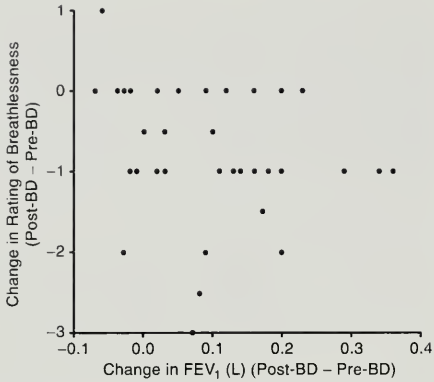

Fig. 1. Relationship of changes in FEV_1 and changes in ratings of breathlessness before and after inhaled bronchodilator (BD) on Day 1 for 37 patients with obstructive airway disease. Spearman's correlation coefficient = −0.26; p = 0.12.

Table 3. Number (Percent) of Patients Showing Improvement and No Improvement in FEV_1 Relative to Breathlessness Ratings on Day 1.

Breathlessness Improved	FEV_1 Improved: No	Yes	Total
No	5 (13.5)	9 (24.3)	14 (37.8)
Yes	4 (10.8)	19 (51.4)	23 (62.2)
Total	9 (24.3)	28 (75.7)	37 (100)

icantly correlated (r = −0.26; p = 0.12, Fig. 1). A 2×2 table (Table 3) shows the number (percent) of patients who did and did not show improvement in breathlessness and FEV_1 on Day 1. Twenty-four patients had concordant results (both spirometry and breathlessness improved or did not change—5 subjects showed no improvement, and 19 subjects exhibited improvements in both FEV_1 and ratings of breathlessness). Discordant results were present in 13 of the 37 patients (35%). These patients showed improvement in one variable but no improvement in the other.

Discussion

The major findings of our study in patients hospitalized for exacerbation of obstructive airway disease are: (1) nebulized albuterol produced significant improvement in spirometry and reduction in breathlessness ratings for all patients (Day 1) and in the subgroup of patients randomized to inhaled albuterol but not in the subgroup randomized to inhaled normal saline (Day 2); (2) there were no significant differences in the absolute changes (post-BD minus pre-BD values) with albuterol therapy between Days 1 and 2 (good reproducibility); and (3) there was no significant correlation between the changes in FEV_1 and the changes in ratings of breathlessness with inhaled albuterol.

These data support the recommended use of inhaled β-2 BD medication for patients hospitalized with an exacerbation of obstructive airways disease. As a group, our patients had severe physiologic impairment as evident by a mean (SD) FEV_1 of 35 (15)% predicted on initial testing. The bronchodilator effect of inhaled albuterol was quite modest as FEV_1 increased by only 80 mL (9.3%) and 102 mL (10.6%) in the two groups on the first day of hospitalization. There are at least two possible explanations for this finding. First, patients had achieved some bronchodilation prior to testing due to previous therapy with inhaled bronchodilators, intravenous corticosteroids, and/or theophylline. Second, over half of our patients had COPD or cystic fibrosis and are known to have a modest response to inhaled BD.

The American Thoracic Society has defined a significant bronchodilator response as at least a 200 mL increase and ≥ 12% improvement in FEV_1 with an inhaled β-2 BD.[8] However, these criteria are intended primarily for testing in outpatients and do not appear to apply to patients who experience acute bronchoconstriction. For example, in 32 patients who experienced an acute exacerbation of COPD, Karpel et al[9] observed that neither metaproterenol (1.95 mg) nor ipratropium bromide (54 μg) administered by MDI with a spacer device significantly improved FEV_1 or FVC after 30 minutes. Of interest, the magnitude of response (~ 100 mL in FEV_1) with metaproterenol was similar to the change observed in our study with nebulized albuterol.

The modest intensities of breathlessness—mean (SD), 3.0 (1.8) and 3.4 (2.4) units—initially reported by the patients presumably represent the benefits of oxygen and BD therapy given in the Emergency Department and/or in the hospital. In two different studies of outpatients with stable COPD, ratings of breathlessness at rest were 3 (median value) in 93 subjects[4] and 2.0 (mean value) in 32 individuals.[10] Although previous studies did not include a placebo trial,[3,4] it is important, if not essential, to incorporate a control arm in the study design, especially when evaluating subjective responses to specific treatment. Based on data from Day 2 of the study, we observed that inhaled BD significantly reduced ratings of breathlessness, whereas inhaled normal saline had no effect. However, the magnitude of change in breathlessness following inhaled BD therapy was less than one unit on the CR-10 scale. Hay et al[10] showed a similar decrease in dyspnea (0.8 units on the CR-10 scale) after inhaled oxitropium bromide, an anticholinergic bronchodilator, in patients with COPD ($p < 0.01$). More detailed analysis of our study indicated that 23 patients (62%) reported some improvement in breathlessness with in-

haled BD treatment on Day 1. These results demonstrate that inhaled albuterol provides an acute but modest decrease in breathlessness in the majority of patients hospitalized with an exacerbation of airways disease. It is interesting that there was no difference in the overall improvement in breathlessness ratings between Days 1 and 2 in the BD group.

Even though albuterol produced significant changes in lung function and breathlessness, the corresponding changes in these variables did not significantly correlate (Fig. 1). These results are consistent with previous data showing that lung function and dyspnea ratings are separate dimensions or constructs in patients with chronic respiratory disease.[11,12] Furthermore, some patients may not perceive or recognize a change in breathlessness with alteration in respiratory function. For example, in a study of stable out-patients with COPD Noseda et al[13] found that 50% (8 of 16) reported significant improvement in shortness of breath after inhaled terbutaline (800 μg) via nebulizer and were considered 'high perceivers,' whereas the other 50% showed no significant response and were called 'low perceivers'; yet, there were no significant differences in FEV_1 or FVC after bronchodilator therapy between the groups. The potential consequences for patients who are poor percievers are serious. Kikuchi et al[14] showed that patients who experienced near-fatal asthma attacks had a blunted perception of dyspnea while breathing through resistive loads.

This collective information emphasizes the importance of measuring subjective ratings as well as physiologic function in evaluating patients with respiratory disease. Symptomatic patients are most concerned about reduction or relief of breathlessness, and therefore routine measurement of dyspnea is appropriate and indicated. Although it is possible to simply ask the patient whether he/she has less, no change, or more breathlessness after inhaled bronchodilator therapy, the use of the CR-10 scale or another measurement instrument enables the health care provider to quantify the subjective response of the patient. For those individuals who may have difficulty in perceiving the intensity of dyspnea or any change, routine measurement of airway function (eg, peak expiratory flow) is important.

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Multisite Evaluation of a Hemoglobin-Based Control for pH and Blood-Gas, Electrolyte, and CO-Oximetry Instruments

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BACKGROUND: Aqueous and fluorocarbon emulsion controls do not have the same oxygen carrying capacity as human blood, and at P_{O_2} levels between 25-100 torr do not adequately assess either analyzer inaccuracy or imprecision. MATERIALS: EQUIL Plus Control (EPC) is a bovine hemoglobin (Hb) solution prepared at 3 levels of Hb and electrolyte concentration (P_{50} range from 26-31 torr). The EQUILibrator Tonometer is a 3-channel bubble tonometer that uses a 6-mL syringe as a tonometry vessel. Tonometry of EPC with appropriate gas mixtures yields clinically relevant values for pH (7.2-7.6), P_{O_2} (40-100 torr), and P_{CO_2} (20-70 torr) and provides clinically useful values for Na^+ (116-160 mmol/L), K^+ (2.9-7.4 mmol/L), iCa^{++} (0.65-1.5 mmol/L), Cl^- (76-120 mmol/L), tHb (90-175g/L), and Hb fractions. EVALUATION METHODS: Tonometered EPC was evaluated on 11 different blood-gas analyzers at 7 sites. Day-to-day imprecision was compared to imprecision obtained with aqueous and fluorocarbon controls. CO-oximetry and electrolyte imprecision were evaluated with EPC only. Post-tonometry stability of blood-gas values was assessed by analysis of 10 samples from a single syringe over 30-minute interval. RESULTS: From 40-100 torr, EPC monitors P_{O_2} inaccuracy within 5% or 3 torr of the theoretical (calculated) value for most analyzers tested. Day-to-day P_{O_2} standard deviations were 35-400% lower than the standard deviations found for aqueous controls in the same P_{O_2} range (on all instruments tested except one). From 20-70 torr, EPC also monitors the P_{CO_2} inaccuracy in most analyzers tested. Imprecision for P_{CO_2} and pH was similar for all 3 types of controls. Electrolyte was generally comparable to aqueous controls. CO-oximetry imprecision was also good for most analyzers tested. Blood-gas values sampled 10 times from a syringe and measured on an ABL 330 changed by < 3% over 30 minutes. CONCLUSION: Tonometered EPC can monitor the P_{O_2} and P_{CO_2} inaccuracy of many blood-gas analyzers and improve the observed P_{O_2} imprecision compared to aqueous controls. EPC electrolyte imprecision was comparable to aqueous controls for iCa^{++}, and K^+, and slightly greater for Na^+. With standard gas mixtures, a single syringe of tonometered EPC can be used on multiple pH and blood-gas and electrolyte instruments for up to 30 minutes. [Respir Care 1995;40(8):820-831]

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Mr Liffmann is employed by Bionostics Inc. His co-authors have no financial interest in Bionostics Inc and received no reimbursement for participation in this study.

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Introduction

The need for improvements in the matrix of commercially available blood-gas quality control materials has been well documented.[1,2] The commonly used aqueous buffers and fluorocarbon emulsions have lower oxygen buffering capacities than whole human blood in the diagnostically important P_{O_2} range of 25-100 torr.[3] As a result, these materials must be handled differently from whole blood and provide P_{O_2} test results that vary by as much as 10-15 torr (at a target value of 50 torr) depending upon the make and model of blood-gas analyzer.[4] These limitations prompted the National Committee for Clinical Laboratory Standards (NCCLS-USA) Sub-Committee on Blood Gas and pH to state that "commercial controls cannot yield a true check for instrument inaccuracy."[5]

The recommended method for assessing the performance of blood-gas measurements is tonometry of leukocyte-poor human blood.[5,6] This advice has not been widely followed because human blood is unstable, nonuniform, metabolically active, and a potential hazard for laboratory workers. The development of a hemoglobin-, or Hb-, based blood substitute for quality control of blood-gas analyzers has, therefore, been actively pursued.[7-9]

Erythrocyte suspensions and hemoglobin solutions equilibrated to known CO_2 and O_2 tensions have been used as control materials.[7,8] However, these products have been shown to have lower P_{50}s (the O_2 tension at which 50% of the functional Hb is HbO_2) than normal human blood,[10,11] and, thus, show inadequate oxygen buffering when compared to normal human blood.[4] Also, formation of methemoglobin in these products may result in unstable P_{O_2} values.[10,11]

EQUIL Plus Control (EPC)* a trilevel, Hb-based, blood-gas, electrolyte, and CO-oximeter control, has been shown to have oxygen buffering properties similar to those of whole human blood.[12] EPC is supplied deoxygenated and is prepared for use by tonometry (ie, by bringing its gas tension to equilibrium with the tensions of a known gas mixture). Previous studies have indicated that tonometered EPC provides blood-gas values that are similar to tonometered human blood.[13] Further studies showed that, like human blood, the Hb solutions had P_{50}s ranging from 26-31 torr.[13] Unlike human blood, however, the pH values for each level after tonometry were found to be predictable and reproducible.[14]

Gas equilibration of EPC can be achieved with commercially available tonometers. However, in this study EQUILibrator Tonometers, specifically designed for use with EPC, were used throughout. According to the manufacturer, the development of this tonometer followed previously published guidelines for achieving proper thermal control (37.0 ± 0.1° C), gas humidification, and complete gas-liquid equilibration.[15] In addition, the tonometer design[16] was altered to minimize evaporation and condensation in EPC to permit the repeatable measurement of pH, electrolytes, and total hemoglobin (tHb).

In this paper, we report the results of a multisite evaluation of tonometered EPC as a control for monitoring the inaccuracy of blood-gas analyzers. In addition, the day-to-day blood-gas, pH, and electrolyte imprecision of tonometered EPC was compared to the imprecision achieved with aqueous and fluorocarbon-based controls. Also, the day-to-day imprecision of tHb and Hb fractions of tonometered EPC was evaluated on 4 different designs or models of CO-oximeter. Finally, post-tonometry stability was evaluated by sequentially testing 10 samples from a single syringe of tonometered EPC for blood-gas values (across a 30-minute period).

Description of the Products

The process for preparing EPC from bovine blood has been previously described by the manufacturer.[17] Stromata are removed from lysed bovine blood by cross-flow filtration through a 0.2 μ filter. The Hb is then deoxygenated, sterile filtered, and subdivided in an atmosphere of N_2-CO_2 gas into glass ampules. The volume of liquid in each ampule is 2.5 ± 0.1 mL. All ampules are stored at temperatures between 2 and 8° C but can be satisfactorily maintained at room temperature for up to 5 days according to the manufacturer. Before use, EPC should be brought to room temperature.

The tonometry system includes a capped, antifoam-treated, 6-mL Monoject syringe. The syringe serves as a tonometry chamber, delivery device, and a storage vessel when capped. A 1.5-in. blunt-tipped needle is mounted on the syringe. An ampule of EPC is opened, and the contents are aspirated from the ampule into the syringe. A gas mixture of known O_2, CO_2, and N_2 composition (%) is warmed, humidified, and bubbled into the sample using a stainless steel probe.

The tonometer is illustrated in Figure 1. The syringe is mounted on the tonometer with the plunger pulled down to the 6-mL mark. The Plexiglas door on the tonometer is closed, pressing the syringe against the heating block of the tonometer. As the sample warms to 37.0 ± 0.1° C (approximately 10 min), the gas flows through the sample and vents through the syringe tip into the atmosphere. The gas flow is controlled by a jeweled orifice and is about 75 mL/min at an inlet pressure of 12 psi.

To verify that EPC is being tonometered at 37.0 ± 0.1° C, a thermocouple calibrated to a thermometer meeting National Institute of Standards and Technology (NIST) specifications is mounted on the rear panel of each tonometer. If the syringe supplied by the manufacturer is used, the thermocouple can be immersed in the liquid being tonometered and the temperature can be monitored to 0.1° C. Thermal adjustments to the operating temperature of the tonometer can be made on the rear panel.

For most studies, 20 minutes is sufficient for gas equilibration, but with larger volumes of EPC (ie, 2 ampules/syringe)

* Suppliers of commercial products are listed in the Products Sources section at the end of the text.

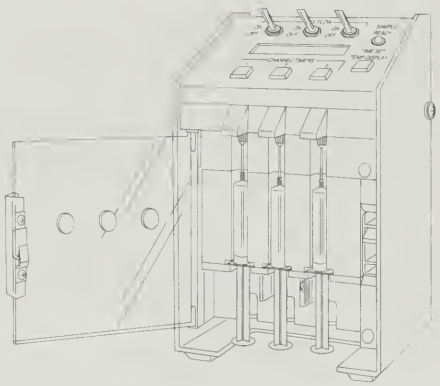

Fig. 1. Sketch of tonometer evaluated for use with hemoglobin-based controls.

longer gas equilibration times are required. After equilibration, the syringe is removed from the tonometer and the gas in the head-space of the syringe is expelled. At ambient temperature, the syringe is capped and transported to instruments for analysis.

Evaluation Methods

Gas Mixtures

Certain gas mixtures are recommended by the manufacturer because after tonometry each level of EPC yields a known pH value. These 'standard' gas mixtures were supplied by Puritan-Bennett, and are shown in Table 1. The gas concentrations were verified by Puritan-Bennett using gas chromatography against NIST traceable gas standards to within 0.03 mole% of the values shown in Table 1. The target values for P_{O_2} and P_{CO_2} are provided in Table 1 with the formula for the target values illustrated in the footnote. At one site, the laboratory staff wanted to use EPC for verification of the upper limit of blood-gas analyzer linearity (ie, P_{O_2} of about 350 torr; P_{CO_2} of about 100 torr). Without this daily verification, the laboratory could not report values above the highest blood-gas-control values analyzed. By using an extended-range gas mixture of 50% O_2, 15% CO_2, balance N_2 to tonometer EPC, they were able to create a high-P_{O_2} and high-P_{CO_2} sample. This concentration was verified by the manufacturer.

Barometric Pressure

At 6 sites, barometric pressure (P_B) was measured daily on mercury barometers, both for calculations used in the study and to verify the internal barometers of the blood-gas instruments. At 1 site, a mercury barometer was not available, and P_B was obtained from the blood-gas analyzer. The accuracy was verified daily by comparison with the P_B obtained from the National Weather Service, which is located at the same altitude and within 10 miles of the participating laboratory.

Table 1. Gas Mixtures Used in Evaluation of Hemoglobin-Based Controls and Tonometer

Gas Mixtures			Tonometered Samples	Target Values*	
% CO_2	% O_2	N_2		P_{CO_2} (torr)	P_{O_2} (torr)
†9.82	14.0	Balance	EQUIL Plus Level 1	70	100
†5.61	9.82	Balance	EQUIL Plus Level 2	40	70
†2.83	5.61	Balance	EQUIL Plus Level 3	20	40
15.0	50.0	Balance	EQUIL Plus Level 1	107	356

* Target values in torr calculated according to the equation

$$\text{target value} = (\text{Gas fraction})(760 - 47)$$

where target values is expressed in torr, 47 = water vapor pressure at 37° C and 760 = barometric pressure at sea level.

† Indicates standard gas mixtures

Evaluation of EPC

Tonometry of EPC. A single ampule of EPC was tonometered for 20-35 minutes. Within 30 minutes after completion of tonometry, EPC was analyzed first on 2 or 3 blood-gas analyzers and then by CO-oximeters, spectrophotometric analyzers capable of determining total Hb and the fractional percentage of each Hb derivative, and stand-alone electrolyte analyzers. For the post-tonometry stability study, 2 ampules from the same EPC level were tonometered together in a single syringe (to provide the sample volume necessary for 10 analyses) for 35-45 minutes. These samples were analyzed 10 times for blood-gas values, within 30 minutes of preparation.

Blood-Gas Inaccuracy. Twice daily for 10 days (at 2 sites the 20 samples were analyzed during an 11-day period), ampules of EPC (Levels 1, 2, and 3) were tonometered with the gases shown in Table 1. The material was then analyzed on the instruments shown in Table 2, and the P_B was recorded. All instruments used in the evaluation were operated according to the manufacturers' specifications. Each laboratory determined the time of day at which the 2 control runs were to be performed and the order in which the controls were to be analyzed. Because the blood-gas values obtained from tonometry are affected by P_B, all blood-gas values were corrected to normal sea-level P_B of 760 torr using the formula based on Henry's Law:

$$(760 - 47)/(P_B - 47)(\text{observed BGV}) = \text{corrected BGV},$$

where BGV = blood-gas value and 47 = the partial pressure (torr) of water vapor at 37° C.

'Normalization' of blood-gas values to 760 torr allows the comparison of blood-gas values obtained from different instruments, at different site elevations, and under different weather conditions to be compared to the target value" (Table 1). The difference between the normalized blood-gas value and the target blood-gas value is what is defined in this paper as blood-gas inaccuracy.

Table 2. pH-Blood Gas and pH-Blood Gas-Electrolyte Analyzers and Aqueous and Fluorocarbon Controls Used in the Evaluation and Comparison

Site	Instruments Used	Control (in ampule)
1	IL 1312	IL ABC Control
	IL BGE	RNA Medical Qualidata 623 Control
2	Radiometer ABL 330	O.T. Blood G.A.S. Control
	NOVA Stat Profile 5*	Stat Profile Control
3	Corning 288†	Ciba Corning Certain + Control
	Corning 288†	Ciba Corning Certain + Control
	Corning 278	Ciba Corning Certain + Control
4	Radiometer ABL 500	RNA Medical Qualidata 123 Control
	Radiometer ABL 500	RNA Med. Qualidata 123 Control
5	IL 1310	RNA Med. Qualidata 623 Control
	Radiometer ABL 505	RNA Med. Qualidata 623 Control
6	Mallinckrodt GEM Premier	GEM Check and Critchek Control
	Mallinckrodt GEM Premier	GEM Check and Critchek Control
7	AVL 995	RNA Med. Qualidata 623 Control
	AVL 995	RNA Med. Qualidata 623 Control

* Electrolyte values were not corrected electronically
† Only Na^+ values were corrected to match flame photometer

Day-to-Day Imprecision of Tonometered EPC, & Aqueous & Fluorocarbon Controls. Twice a day for 10 days either aqueous or fluorocarbon controls and tonometered EPC were analyzed for pH, blood gases, and, in some cases, electrolytes. Tonometered EPC samples were prepared, analyzed, and the values corrected for P_B as we have described. (At 1 site, a total of 20 aqueous controls were analyzed over the course of 8 days. The 8 days fell on the same days that tonometered EPC samples were analyzed. From 1 to 4 aqueous blood-gas controls were analyzed. At 2 other sites, the 20 controls were analyzed during a period of 11 days.)

Aqueous or fluorocarbon-based controls in ampules were used according to the established procedures of each laboratory. Four laboratories discarded each ampule after a single use on only 1 blood-gas analyzer, whereas 3 laboratories used special devices supplied by the analyzer manufacturer or a syringe to inject the control into 1 or more analyzers. The blood-gas and pH and combination blood-gas and pH and electrolyte analyzers and the aqueous and fluorocarbon controls used in this study are shown in Table 2.

Day-to-Day Electrolyte & CO-Oximetry Imprecision. Twice daily for 10 days tonometered EPC was analyzed for electrolytes, tHb, and Hb fractions on the instruments shown in Table 3. Tonometered EPC samples were prepared and analyzed as described earlier.

Table 3. Instruments Used To Evaluate Tonometered EPC as an Electrolyte and CO-Oximeter Control

Site	Electrolyte Analyzers	CO-Oximeter Analyzers
1	IL BGE*	AVL 912
	AVL 984†	
3	None	Corning 2500
4	None	Radiometer OSM3
5	NOVA 6†	IL 282
	Radiometer ABL 505	Radiometer OSM3
6	Mallinckrodt GEM Premier (1)†	None
	Mallinckrodt GEM Premier (2)†	None
7	None	AVL 912

* Na^+ and K^+ values were readjusted to match flame photometer.
† Electrolyte values were not corrected electronically.

Post-Tonometry Blood-Gas Stability. Tonometered EPC samples were prepared as described previously, except for 2 ampules from each level of EPC that were tonometered in a single syringe. After tonometry, those samples of EPC were analyzed 10 sequential times on the same blood-gas analyzer, during a 30-minute period. Between each analysis, air in the syringe head-space was expelled, and the syringe was recapped. All values were also corrected for P_B.

Statistical Methods. The imprecision of all measurements of tonometered EPC and of aqueous and fluorocarbon controls was evaluated from the means and standard deviations calculated from the day-to-day imprecision data.[18] Using the method described in Tietz,[19] all highly statistically significant outliers ($p < 0.01$) were eliminated from the database and were not used in the analysis of imprecision.

The elimination of any data point is either noted in the table or is reflected in a decreased n value for that group of data.

Evaluation Results

Blood-Gas Inaccuracy

Figures 2 and 3 illustrate the P_{O_2} and P_{CO_2} recovery of 11 different blood-gas analyzers, from 6 different manufacturers, at 7 different sites using tonometered EPC. Table 4 illustrates the P_{O_2} and P_{CO_2} recovery of 2 different blood-gas analyzers, from a single manufacturer, at 1 site, using EPC (Level 1) tonometered to elevated P_{O_2} (356 torr) and P_{CO_2} (107 torr) target values.

Day-to-Day pH, Blood-Gas, & Electrolyte Imprecision

Site-to site comparisons of means and standard deviations

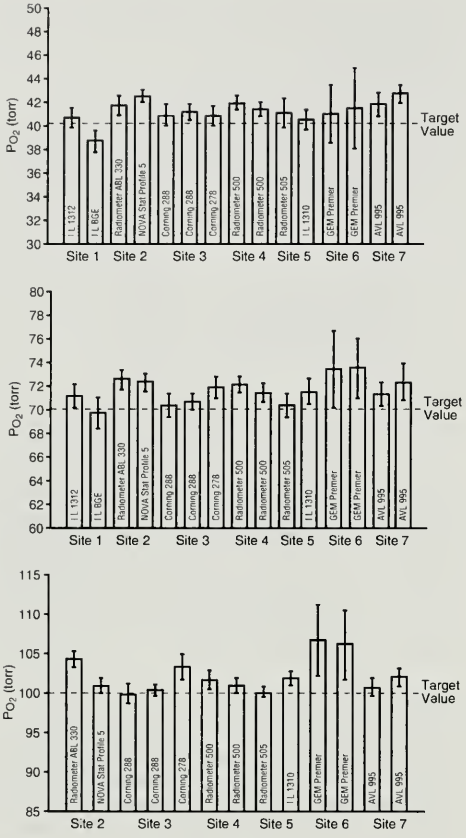

Fig. 2A-2C. Graphs of P_{O_2} accuracy of blood-gas analyzers, using tonometered hemoglobin-based control (Equil Plus). Twenty samples were tonometered at 3 levels (P_{O_2} 40 torr, 70 torr, and 100 torr) during a 10-day period. Two samples were analyzed each day on the instruments identified in each figure. The error bars represent ± 1 standard deviation.

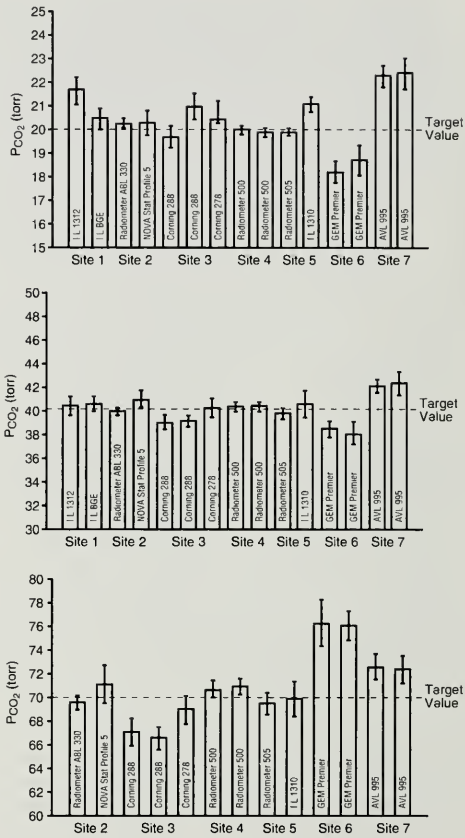

Fig. 3A-3C. Graphs of P_{CO_2} accuracy of blood-gas analyzers, using tonometered hemoglobin-based control (Equil Plus). Twenty samples were tonometered at 3 levels (P_{CO_2} 20 torr, 40 torr, and 70 torr) during a 10-day period. Two samples were analyzed each day on the instruments identified in each figure. The error bars represent ± 1 standard deviation.

Table 4. Accuracy of Tonometered EPC at Elevated P_{O_2} and P_{CO_2} Values

Instrument	Variable	Target Value (torr)	Mean (torr)*	n
IL BGE	P_{O_2}	356.5	357.0	20
IL 1312	P_{O_2}	356.5	347.8	20
IL BGE	P_{CO_2}	106.9	106.9	20
IL 1312	P_{CO_2}	106.9	100.7	19

* Mean values 'normalized' to a barometric pressure of 760 torr (ie, normal sea level).

from the analysis of tonometered EPC and controls for P_{O_2}, P_{CO_2}, pH, and electrolytes are shown in Tables 5-8.

Day-to-Day Imprecision of Electrolytes, tHb, & tHb Fractions

Site-to-site comparisons of means and standard deviations from the analysis of tonometered EPC for electrolytes, tHb and Hb fractions are shown in Tables 9 and 10.

Table 5. P_{O_2} Day-to-Day Imprecision of Instruments Using Tonometered EPC and Aqueous or Fluorocarbon Controls

Site	Instrument	Type Control	Mean (SD) Gas Tensions in torr High O_2	Normal O_2	Low O_2	Critical O_2*
1	IL 1312	Fluorocarbon	145 (1.4)	——	54 (1.6)	——
		EPC†	348 (4.1)	——	71 (1.0)	41 (0.7)‡
1	IL BGE	Aqueous	135 (1.3)	100 (1.6)	61 (2.7)	——
		EPC†	357 (6.1)	——	70 (1.3)	39 (0.9)‡
2	ABL 330	Aqueous	154 (3.0)	104 (2.2)	60 (1.5)	——
		EPC	——	104 (1.0)	73 (0.9)	42 (0.8)
2	Nova Stat Profile 5	Aqueous	144 (2.8)	99 (2.6)	61 (1.3)	——
		EPC	——	101 (0.9)	72 (0.7)	42 (0.5)
3	Corning 288 (1)	Aqueous	149 (3.3)	104 (2.2)	67 (3.6)	——
		EPC	——	100 (1.2)	70 (1.0)	41 (0.9)
3	Corning 288 (2)	Aqueous	151 (2.7)	104 (2.3)	66 (3.0)	——
		EPC	——	100 (0.7)	71 (0.7)	41 (0.7)
3	Corning 278	Aqueous	156 (3.1)	107 (3.1)	67 (5.3)	——
		EPC	——	103 (1.6)	72 (0.9)	41 (0.8)
4	Radiometer 500(1)	Aqueous	153 (2.6)	108 (2.1)	70 (2.0)‡	——
		EPC	——	101 (0.9)	72 (0.7)	42 (0.6)
4	Radiometer 500(2)	Aqueous	153 (1.8)	107 (2.4)	70 (3.5)	——
		EPC	——	101 (1.2)	71 (0.8)	41 (0.6)
5	Radiometer 505	Aqueous	155 (3.4)	111 (2.5)	73 (4.6)	——
		EPC	——	100 (0.7)	70 (0.9)	41 (1.2)
5	IL 1310	Aqueous	156 (3.2)	114 (4.5)	74 (6.2)	——
		EPC	——	102 (1.0)	72 (1.2)	41 (0.8)
6	Mallinckrodt GEM Premier (1)	Aqueous	150 (3.3)	101 (4.1)	60 (3.1)	——
		EPC§	——	106 (4.6)	73 (3.3)	40 (2.4)
6	Mallinckrodt GEM Premier (2)	Aqueous	149 (4.0)	100 (3.5)	59 (2.7)	——
		EPC§	——	106 (4.4)‡	74 (2.6)	41 (3.4)
7	AVL 995 (1)	Aqueous	147 (2.1)	111 (5.0)	69 (3.1)	——
		EPC	——	101 (1.0)	71 (1.0)	42 (0.9)
7	AVL 995 (2)	Aqueous	147 (2.4)‡	111 (3.0)‡	75 (4.3)	——
		EPC	——	102 (1.1)	72 (1.5)	43 (0.6)

* The P_{O_2} at which clinician action is indicated because of the likelihood of hypoxemia in the patient
† Special gas mixture used with Level-1 EPC
‡ One outlier
§ Only 19 samples of EPC prepared and analyzed

Post-Tonometry Blood-Gas Stability

Figures 4A and 4B show the change in P_{O_2} and P_{CO_2} values for 10 sequential injections of tonometered EPC into an ABL 330 blood-gas analyzer during a 30-minute period. Three levels of P_{O_2} and P_{CO_2} values were tested. Figures 4C and 4D show the results of the same test series on an IL 1312. In this case, however, the samples were aspirated into the analyzer, and Level-1 EPC was tonometered with the extended-range gas mixture.

Discussion

Previous studies have compared erythrocyte suspensions and hemoglobin solutions pre-equilibrated to known P_{CO_2} and P_{O_2} tensions with aqueous and fluorocarbon-based controls for P_{O_2} imprecision. The results of these studies indicated either no improvement or an increase in imprecision for P_{O_2} measurements with the Hb-based materials.[2,10,11] The explanations for the increased P_{O_2} imprecision of the Hb-based controls were (1) the P_{50}s were lower than in normal human blood, resulting in a loss of the oxygen buffering capacity of the Hb; (2) the formation of methemoglobin as the products aged caused a decrease in the active Hb and P_{50} value, and a steady increase in the measured P_{O_2} value; and (3) the products were sensitive to temperature and operator handling.[2,10,11]

In contrast, the day-to-day P_{O_2} standard deviations of tonometered EPC were less than the standard deviations found with aqueous control materials in the range of 40-100 torr (Table 5) for all analyzers tested except the Mallinckrodt GEM Premier. In the one site at which EPC was compared to a fluorocarbon control in the same P_{O_2} range noted, the tonometered EPC had a smaller standard deviation. The improved imprecision found with tonometered EPC is probably due to (1) the methemoglobin remains low throughout the 18-month shelf life of the EPC because all Hb is in a deoxygenated form;

Table 6. P_{CO_2} Day-to-Day Imprecision of Instruments Using Tonometered EPC and Aqueous or Fluorocarbon Controls

Site	Instrument	Control	Mean (SD) CO_2 Tensions in torr High CO_2	Normal CO_2	Low CO_2
1	IL 1312	Fluorocarbon	64.2 (1.2)	— —	23.6 (0.6)
		EPC*	100.7 (1.1)†	40.4 (0.8)	21.7 (0.6)
1	IL BGE	Aqueous	69.3 (0.8)	43.6 (0.4)	22.2 (0.2)
		EPC*	106.9 (2.2)	40.6 (0.7)	20.5 (0.4)
2	ABL 330	Aqueous	62.8 (0.7)	36.0 (0.3)	18.4 (0.2)
		EPC	69.9 (0.6)	39.9 (0.3)	20.3 (0.2)
2	Nova Stat Profile 5	Aqueous	64.4 (2.0)	40.6 (0.9)	22.0 (0.6)
		EPC	71.2 (1.7)	40.9 (0.7)	20.3 (0.5)
3	Corning 288 (1)	Aqueous	69.7 (1.1)	43.5 (0.7)	22.0 (0.4)
		EPC	67.1 (1.1)	39.0 (0.5)	19.7 (0.5)
3	Corning 288 (2)	Aqueous	69.8 (1.1)	44.2 (0.8)	23.4 (0.4)
		EPC	66.6 (1.0)	39.1 (0.5)	21.0 (0.5)
3	Corning 278	Aqueous	71.1 (1.0)	44.8 (0.6)	23.1 (0.7)
		EPC	69.0 (1.1)	40.2 (0.8)	20.8 (0.4)
4	Radiometer 500(1)	Aqueous	62.2 (0.5)	35.8 (0.3)	18.4 (0.2)
		EPC	70.7 (0.7)	40.3 (0.4)	20.0 (0.2)†
4	Radiometer 500(2)	Aqueous	62.1 (0.7)	35.7 (0.4)	18.1 (0.2)
		EPC	71.0 (0.7)	40.3 (0.4)	19.9 (0.2)
5	Radiometer 505	Aqueous	63.3 (0.8)†	36.6 (0.4)†	18.6 (0.4)
		EPC	69.5 (0.9)	39.7 (0.4)	19.9 (0.2)
5	IL 1310	Aqueous	61.6 (2.4)	36.9 (1.2)	20.2 (0.7)
		EPC	69.9 (1.5)	40.5 (1.1)	21.1 (0.3)
6	Mallinckrodt GEM Premier (1)	Aqueous	73.1 (3.7)	36.5 (0.8)	17.2 (1.4)
		EPC‡	76.3 (2.0)	38.4 (0.7)	18.2 (0.5)
6	Mallinckrodt GEM Premier (2)	Aqueous	73.0 (3.4)	36.9 (0.8)	17.3 (1.6)
		EPC‡	76.1 (1.3)	38.0 (0.9)	18.7 (0.6)
7	AVL 995(1)	Aqueous	71.9 (1.4)	45.4 (0.8)	24.0 (0.5)
		EPC	72.6 (1.1)	42.0 (0.6)	22.3 (0.5)
7	AVL 995(2)	Aqueous	70.5 (1.5)	45.5 (0.7)†	24.3 (0.9)
		EPC	72.4 (1.2)†	42.2 (1.0)	22.4 (0.6)

* Special gas mixture used with Level-1 EPC
† One outlier
‡ Only 19 samples of EPC prepared and analyzed

(2) the P_{50} of EPC is in the same range as normal human blood and remains stable for the product's shelf life; (3) the temperature during tonometry is regulated to 37.0 ± 0.1° C; and (4) EPC is tonometered in a syringe so that all the gas headspace can be eliminated before the syringe is capped.

P_{CO_2} day-to-day imprecision for EPC was similar to the results obtained with aqueous and fluorocarbon controls for nearly all the instruments tested (Table 6). The only exception was the Mallinckrodt GEM Premier, for which P_{CO_2} standard deviations for tonometered EPC were generally smaller than the standard deviations for aqueous controls (Table 6). Day-to-day pH imprecision was essentially the same for all the controls tested on the different analyzers (Table 7). Table 8 indicates that aqueous controls and tonometered EPC have similar day-to-day imprecision for iCa^{++} and K^+, but the Na^+ imprecision was lower for aqueous controls on the Corning 288 and on the NOVA Stat Profile 5. Table 9 shows that on a variety of electrolyte analyzers tonometered EPC can provide low day-to-day imprecision (the Na^+ imprecision may be higher than the imprecision obtained from aqueous controls). The greater Na^+ imprecision may be caused by the high protein levels in EPC or small changes in the sample from condensation or evaporation during tonometry. In some cases operator error, such as overfilling the gas humidification cups (which may result in the humidification solution's diluting the EPC), and failing to introduce the tonometry gas (to expel residual condensation in the stainless steel probe) before placing the syringe of EPC on the tonometer may also have led to greater Na^+ imprecision. The day-to-day CO-oximeter imprecision (for tHb and HbO_2%) shown in Table 10 for tonometered EPC was excellent for the AVL 912, the IL 282, and for 1 Radiometer OSM3 tested. The Corning 2500 and another OSM 3 gave results that were less precise. The OSM 3 with the greater imprecision was adjusted by the users so that the values it gave for whole-blood samples matched the IL 282. The small percentage (< 2.0%) of COHb found in tonometered EPC varied considerably from one CO-oximeter to another (Table 10). This was

Table 7. pH Day-to-Day Imprecision of Instruments Using Tonometered EPC and Aqueous or Fluorocarbon Controls

Site	Instrument	Control	Mean (SD) Values for pH Acidosis	Normal	Alkalosis
1	IL 1312	Fluorocarbon	7.22 (0.005)	— —	7.60 (0.005)
		EPC*	7.10 (0.003)	7.40 (0.003)	7.60 (0.004)
1	IL BGE	Aqueous	7.15 (0.004)	7.41 (0.004)	7.61 (0.004)
		EPC*	7.10 (0.004)	7.39 (0.005)	7.59 (0.006)
2	ABL 330	Aqueous	7.12 (0.003)	7.41 (0.004)	7.63 (0.005)
		EPC	7.20 (0.003)	7.40 (0.004)	7.59 (0.004)
2	Nova Stat Profile 5	Aqueous	7.14 (0.004)	7.36 (0.003)	7.57 (0.003)
		EPC	7.20 (0.003)	7.40 (0.003)	7.59 (0.003)
3	Corning 288 (1)	Aqueous	7.15 (0.004)	7.40 (0.006)	7.60 (0.005)
		EPC	7.19 (0.003)	7.39 (0.004)	7.59 (0.003)
3	Corning 288 (2)	Aqueous	7.15 (0.004)	7.41 (0.004)	7.60 (0.005)
		EPC	7.20 (0.004)	7.40 (0.003)	7.59 (0.004)
3	Corning 278	Aqueous	7.15 (0.004)	7.40 (0.005)	7.60 (0.005)
		EPC	7.20 (0.003)	7.39 (0.004)	7.58 (0.003)
4	Radiometer 500(1)	Aqueous	7.12 (0.001)	7.41 (0.002)	7.62 (0.004)
		EPC	7.19 (0.003)†	7.39 (0.003)	7.59 (0.003)
4	Radiometer 500(2)	Aqueous	7.12 (0.002)	7.41 (0.002)	7.62 (0.004)†
		EPC	7.18 (0.002)†	7.38 (0.003)	7.58 (0.002)
5	Radiometer 505	Aqueous	7.11 (0.003)	7.40 (0.000)	7.62 (0.007)
		EPC	7.19 (0.005)	7.39 (0.003)	7.59 (0.003)
5	IL 1310	Aqueous	7.12 (0.005)	7.41 (0.005)	7.63 (0.006)
		EPC	7.19 (0.005)	7.39 (0.005)†	7.59 (0.004)
6	Mallinckrodt GEM Premier (1)	Aqueous	7.02 (0.009)	7.38 (0.003)	7.60 (0.004)
		EPC‡	7.10 (0.006)	7.35 (0.010)	7.60 (0.009)
6	Mallinckrodt GEM Premier (2)	Aqueous	7.02 (0.008)	7.38 (0.005)	7.60 (0.009)
		EPC‡	7.10 (0.006)	7.35 (0.009)	7.59 (0.010)
7	AVL 995(1)	Aqueous	7.14 (0.003)†	7.39 (0.004)	7.60 (0.005)
		EPC	7.19 (0.004)	7.39 (0.004)	7.58 (0.005)
7	AVL 995(2)	Aqueous	7.14 (0.006)	7.39 (0.005)	7.60 (0.005)
		EPC	7.18 (0.006)	7.39 (0.007)	7.58 (0.006)

* Special gas mixture used with Level-1 EPC
† One outlier
‡ Only 19 samples of EPC prepared and analyzed

not surprising because it has been shown that all the CO-oximeters used in this study could not accurately or reliably measure low concentrations (< 5.0%) of COHb.[20] Having a higher COHb% might make tonometered EPC a more useful CO-oximeter control.

Clausen and Murray[21] have suggested that P_{O_2} measurements in the critical lower range should be accurate to within 3 torr of the target value. The results of our study suggest that all the blood-gas analyzers monitored with tonometered EPC in the P_{O_2} range of 40-70 torr either meet or almost meet this criterion (Figs. 2A & 2B). As indicated by Figure 2C and Table 3, tonometered EPC also monitors the P_{O_2} inaccuracy (within 5%) at 100 and 356 torr for nearly all the analyzers tested.

The inaccuracy of P_{CO_2} measurements should also be within 3 torr of the actual value, according to Clausen and Murray.[21] As indicated by Figures 3A-3C, tonometered EPC monitors the P_{CO_2} inaccuracy in all the analyzers tested except the GEM Premier, which at a target of 70 torr was 6 torr high. At elevated P_{CO_2} values (> 105 torr), the IL BGE recovered the target P_{CO_2} (within 5%) value in tonometered EPC whereas the IL 1312 was 6% low (Table 4).

Also, because EPC has active Hb to buffer any P_{O_2} changes but no leukocytes to consume oxygen,[22] the P_{O_2} gas values of EPC are stable when stored at room temperature in a capped plastic syringe. Figures 4A and 4B indicate that 10 sequential injections of EPC Levels 1, 2, and 3 (tonometered with standard gases) into a Radiometer ABL 330 (during a 30-minute period) result in less than a 3% change in the initial P_{O_2} and P_{CO_2} values.

Some blood-gas instruments aspirate the sample from the syringe (eg, IL 1312). In these cases, air replaces the liquid that is removed from the syringe. This air is a source of oxygen that can contaminate the control liquid. When 10 sequential aspirations of an EPC Level-1 sample (tonometered with an extended-range gas) are introduced into an IL 1312, both the P_{O_2} and P_{CO_2} values change by more than 3% after 3 aspirations (Figs. 4C & 4D). With tonometered Level-2 EPC, the P_{O_2} value

Table 8. Mean (SD) Electrolyte Values (in mmol) Reflecting Day-to-Day Imprecision of Different Instruments with Aqueous and Tonometered EPC Controls

Instrument	Level	Control	Na^+	K^+	iCa^{++}
Nova Stat Profile 5	1	Aqueous	158.5 (0.64)	5.77 (0.06)	1.467 (0.010)
		EPC	152.9 (0.65)	7.33 (0.06)	1.420 (0.016)
	2	Aqueous	138.2 (0.60)	3.83 (0.05)	0.986 (0.009)
		EPC	139.4 (0.70)	5.20 (0.04)	1.067 (0.010)
	3	Aqueous	120.2 (0.48)	2.00 (0.05)	0.566 (0.007)
		EPC	117.9 (0.52)	3.01 (0.02)	0.729 (0.005)
Corning 288(1)	1	Aqueous	151.9 (0.53)	7.23 (0.12)	0.671 (0.023)
		EPC	153.4 (1.38)	7.68 (0.10)	1.462 (0.018)
	2	Aqueous	137.3 (0.44)	4.82 (0.07)	1.161 (0.019)
		EPC	142.2 (1.55)	5.30 (0.08)	1.074 (0.014)
	3	Aqueous	121.2 (0.79)	2.71 (0.05)	1.578 (0.023)
		EPC	123.3 (1.67)	2.97 (0.06)	0.719 (0.018)
Corning 288(2)	1	Aqueous	151.5 (0.76)	7.16 (0.11)	0.665 (0.015)
		EPC	150.2 (1.12)	7.71 (0.06)	1.444 (0.018)
	2	Aqueous	136.8 (0.52)	4.72 (0.06)	1.169 (0.011)
		EPC	139.9 (1.13)	5.23 (0.07)	1.065 (0.010)
	3	Aqueous	120.3 (0.66)	2.69 (0.06)	1.598 (0.015)
		EPC	121.9 (1.64)	2.90 (0.06)	0.720 (0.013)

Table 9. Mean (SD) Electrolyte Values (in mmol) Reflecting Day-to-Day Imprecision of Tonometered EPC on Different Instruments

Instrument	Level	Na^+	K^+	iCa^{++}
IL BGE	1	151.6 (1.19)	7.38 (0.12)	1.67 (0.035)*
	2	138.2 (1.96)	5.17 (0.11)*	1.19 (0.016)*
	3	116.5 (0.83)	3.01 (0.06)	0.77 (0.012)
AVL 984	1	159.4 (1.14)	7.56 (0.08)	1.58 (0.011)
	2	145.2 (1.45)	5.29 (0.04)	1.14 (0.009)
	3	120.4 (0.93)	3.04 (0.04)	0.72 (0.009)*
Nova 6	1	154.9 (0.94)	7.41 (0.09)	1.46 (0.011)
	2	140.9 (0.64)	5.19 (0.04)	1.07 (0.016)
	3	118.5 (1.36)	3.01 (0.03)	0.72 (0.010)
Radiometer 505	1	150.7 (0.95)	7.44 (0.10)	1.51 (0.010)
	2	137.1 (1.04)	5.18 (0.04)	1.10 (0.024)
	3	116.2 (1.47)*	2.98 (0.05)	0.71 (0.018)
Mallinckrodt GEM Premier (1)†	1	161.3 (1.60)	7.28 (0.06)	1.50 (0.024)*
	2	146.3 (0.84)	5.12 (0.03)	1.07 (0.026)
	3	121.7 (0.85)	2.97 (0.03)	0.68 (0.016)*
Mallinckrodt GEM Premier (2)†	1	160.6 (2.08)	7.37 (0.08)	1.51 (0.034)
	2	146.0 (0.86)	5.19 (0.05)	1.07 (0.022)
	3	121.8 (1.01)	2.99 (0.03)	0.67 (0.010)

* One outlier

† Only 19 samples of EPC were prepared and analyzed

changes by 4% after the seventh aspiration into the 1312. The ninth and tenth aspirations were only 2.8% higher than the initial value. The blood-gas values of tonometered Level 3 are stable for all 10 aspirations. Because tonometered Level-3 EPC contains the highest percentage of deoxyhemoglobin, this result was not unexpected.

Throughout the study the GEM Premier appeared to produce more imprecise and inaccurate blood gas analyses than did the other analyzers. Because the calibration procedure and the electrochemical sensors in the GEM Premier are different from the other analyzers,[23] it is possible that the tonometered Hb solution causes interference with the P_{CO_2} and P_{O_2} measurements. More extensive studies are required to understand this phenomenon.

Two additional difficulties with the study were (1) the aqueous and fluorocarbon controls and tonometered EPC were not

Table 10. Mean (SD) CO-Oximetry Values Reflecting Day-to-Day Imprecision of Tonometered EPC on Different Instruments

Instrument	Level	tHb(g/dL)	HbO_2%	COHb%	MetHb%
AVL 912 (1)	1	17.4 (0.07)	96.9 (0.32)	0.12 (0.20)	1.48 (0.23)
	2	13.8 (0.11)	93.5 (0.47)	0.96 (0.19)	1.46 (0.28)
	3	8.8 (0.06)	87.3 (1.00)	0.55 (0.24)	1.58 (0.27)
Corning 2500	1	17.4 (0.35)	96.7 (0.53)	0.0 (0.0)	1.30 (0.30)
	2	13.9 (0.31)	95.4 (0.76)	0.86 (0.15)	0.94 (0.31)
	3	9.0 (0.22)	89.8 (1.58)	1.64 (0.13)	0.80 (0.26)
Radiometer OSM3 (1)	1	18.2 (0.10)	95.6 (0.35)*	1.66 (0.11)*	1.26 (0.16)*
	2	14.7 (0.04)	94.5 (0.44)	1.57 (0.11)	1.31 (0.16)
	3	9.8 (0.04)	88.4 (0.54)	1.32 (0.11)	1.14 (0.31)
IL 282	1	17.8 (0.22)	94.7 (0.25)	1.54 (0.14)	1.19 (0.30)
	2	14.2 (0.17)	93.2 (0.28)	2.59 (0.15)	1.29 (0.30)
	3	9.1 (0.11)	86.4 (0.48)	3.15 (0.24)	1.34 (0.42)
Radiometer OSM3† (2)	1	19.0 (0.43)	97.3 (0.15)	1.61 (0.08)	1.08 (0.20)
	2	15.4 (0.28)	96.6 (0.25)	1.76 (0.08)	1.09 (0.21)
	3	10.2 (0.18)	90.3 (0.84)	1.65 (0.10)	1.01 (0.11)
AVL 912 (2)	1	17.3 (0.05)	93.3 (0.21)	1.31 (0.10)	1.30 (0.18)
	2	13.7 (0.06)	94.2 (0.51)	1.26 (0.15)	1.13 (0.16)
	3	8.8 (0.05)	88.5 (0.37)	0.46 (0.11)	1.19 (0.12)

* One outlier

† Instrument adjusted by user to read as the IL 282 did.

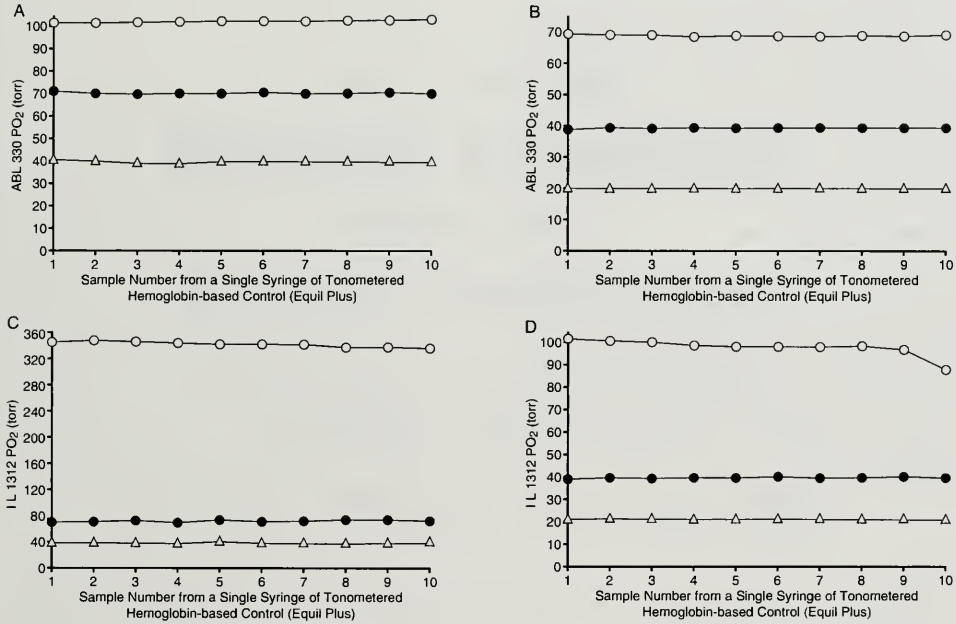
A
ABL 330 PO2 (torr)
Sample Number from a Single Syringe of Tonometered Hemoglobin-based Control (Equil Plus)
B
ABL 330 PO2 (torr)
Sample Number from a Single Syringe of Tonometered Hemoglobin-based Control (Equil Plus)
C
I L 1312 PO2 (torr)
Sample Number from a Single Syringe of Tonometered Hemoglobin-based Control (Equil Plus)
D
I L 1312 PO2 (torr)
Sample Number from a Single Syringe of Tonometered Hemoglobin-based Control (Equil Plus)

Fig. 4 A-D. Post-tonometry blood-gas stability of hemoglobin-based control. Two ampules of hemoglobin-based control (Equil Plus) were tonometered in a single syringe for 35-45 minutes. After tonometry, each sample was either injected 10 times into a Radiometer ABL 330 or aspirated 10 times into an IL 1312. Numbers on horizontal axis are sample numbers from a single syringe. Fig 4A illustrates the P_{O_2} and 4B the P_{CO_2} post-tonometry stability of the hemoglobin-based control on the ABL 330 for Level 1 (o—o), Level 2 (●——●), and Level 3 (△—△). Fig. 4C illustrates the P_{O_2} and 4D the P_{CO_2} post-tonometry stability as analyzed by the IL 1312 for Level-1 (o—o) extended range gas mixture, Level 2 (●——●), and Level 3 (△—△).

analyzed randomly or at specific times each day, and (2) because one site did not have a barometer to check the built-in barometers of the blood-gas instruments, both the blood-gas readings and the calculations used to normalize the blood-gas readings might have more error associated with them than those of the other sites.

Additional studies are planned with EPC to evaluate whether (1) the improved P_{O_2} imprecision of tonometered EPC tests can statistically justify a reduction in blood-gas quality control testing, (2) EPC can be tonometered twice without losing its effectiveness as a combination control, and (3) EPC compares favorably with other control materials for instrument error detection of CO-oximetry and electrolyte analyzers.

Conclusions

We have demonstrated that EPC can be used to monitor the P_{O_2} and P_{CO_2} inaccuracy between 40-100 and 20-70 torr on a variety of blood-gas analyzers. We have also demonstrated that on some blood-gas analyzers tonometered EPC can monitor P_{O_2} inaccuracy at 356 torr and P_{CO_2} inaccuracy at 107 torr.

In addition, our data suggest that the day-to-day P_{O_2} imprecision in the 40-100 torr range is better with tonometered EPC than with aqueous controls on nearly all of the analyzers tested. The pH and P_{CO_2} imprecision with EPC was as good as that obtained with aqueous or fluorocarbon-based blood-gas controls. Day-to-day electrolyte imprecision with tonometered EPC seemed to be about as good as aqueous controls for K^+ and iCa^{++}, but not as good for Na^+. The CO-oximeter imprecision results were somewhat variable. On 4 of the 6 analyzers tested, the imprecision was good, but the other 2 gave more variable tHb results.

Because the number of useful blood-gas control measurements that can be made from a single syringe of tonometered EPC depends on different variables, post-tonometry stability experiments should be interpreted conservatively. We believe that for best results (using standard gas mixtures), tonometered EPC should be used within 30 minutes of preparation on a maximum of 3 to 5 blood-gas analyzers. This would allow the user to monitor multiple pH and blood-gas and pH and blood-gas and electrolyte analyzers with a single ampule of tonometered EPC.

PRODUCT SOURCES

Controls:
- EQUIL™ Plus Control, Qualidata™ 123, Qualidata 623, RNA Medical Division of Bionostics IC, Acton MA
- ABC™ Control, Instrumentation Laboratory IC, Lexington MA
- Stat Profile™ Control, NOVA Biomedical, Waltham MA
- Certain™ +, Ciba Corning Diagnostics IC, Medfield MA
- Blood G.A.S. Control™, Organon Teknika Corp, Durham NC
- GEM™ Check and GEM Critchek, Mallinckrodt Sensor Systems, Ann Arbor MI

Tonometer:
- EQUILibrator™, RNA Medical Division of Bionostics IC, Acton MA

Combination Analyzers:
- IL 1310, 1312, and BGE™, Instrumentation Laboratory, Lexington MA
- Corning 278 and 288, Ciba Corning Diagnostics, Medfield MA
- Radiometer ABL™ 330, 500, and 505, Radiometer A/S Copenhagen Denmark
- Mallinckrodt GEM Premier, Mallinckrodt Sensor Systems, Ann Arbor MI
- NOVA Stat Profile 5, NOVA Biomedical, Waltham MA
- AVL 995, AVL Scientific Corp, Roswell GA

Electrolyte Analyzers:
- AVL 984, AVL Scientific Corp, Roswell GA
- NOVA 6, NOVA Biomedical, Waltham MA

CO-Oximeters:
- IL 282, Instrumentation Laboratory, Lexington MA
- Corning 2500, Ciba Corning Diagnostics, Medfield MA
- AVL 912, AVL Scientific Corp, Roswell GA
- OSM3, Radiometer A/S, Copenhagen, Denmark

Syringes & Needles:
- Sherwood Medical, St Louis MO

Tonometry Gases:
- Puritan-Bennett, Marlborough MA
- Holox, Union City GA

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Pulmonary Disease in AIDS: Implications for Respiratory Care Practitioners

Debra L Medin BS RRT and Frederick P Ognibene MD

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Introduction

The awareness of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) is into its second decade, and respiratory care practitioners are increasingly called upon to care for those with this disease.

Since the syndrome was first described in 1981, knowledge has been gained and made available to health-care workers involved in the care of patients with AIDS. Because the lungs are either a primary site of infection or the portal of entry for many life-threatening infections in AIDS, and because 65% of AIDS-defining illnesses are pulmonary opportunistic infections,[1,2] respiratory care professionals must become as familiar as possible with this disease.

In this review, we present the variety of pulmonary infections and diseases common in patients with HIV infection. Pathophysiology is described, and the differences between pediatric and adult care are highlighted. Further, we examine the role of respiratory care practitioners in the diagnosis of pulmonary diseases and also discuss current therapies, ef-

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ficacy issues, safety in the workplace, and ethical issues. Finally, we explore the future role of respiratory care practitioners in the care of the patient with AIDS.

Adult Pulmonary Disease

Pneumocystis carinii Pneumonia

Pneumocystis carinii (*P. carinii*) pneumonia is the most common of the pulmonary complications of AIDS. In at least 60% of AIDS patients, *P. carinii* pneumonia is the first manifestation of illness, and up to 85% of those with the syndrome contract the disease.[3] Further, as many as one quarter of patients with AIDS die from complications of this pneumonia.

P. carinii is an opportunistic pathogen first identified in malnourished infants during World War II.[4] The small number of cases reported each year before the AIDS epidemic began typically involved patients with primary immunodeficiencies, cancer patients receiving chemotherapy, and organ-transplant recipients. These conditions share a defect in T-cell immunity that predisposes the host to certain opportunistic infections. An important factor predisposing the AIDS patient to *P. carinii* pneumonia is a decline in the number of T-helper ($CD4^+$) lymphocytes in the blood to fewer than 20% of total T lymphocytes or an absolute number of fewer than 200 cells/mm^3.[5] The $CD4^+$ lymphocyte count is also a predictor of the progression of HIV infection to AIDS[6] because the human immunodeficiency virus is responsible for the reduction of these cells.

P. carinii was once considered to be a protozoan; however, recent examination of the organism has determined that it is more similar to a fungus or an ascomycete.[7-10] The organism has a predilection for the lung and possibly is transmitted via aerosolization. It has also been found in the soil.[4] *P. carinii* is ubiquitous, and many immunologically competent children are exposed to the organism but never develop pulmonary symptoms. In studies conducted in the mid-1970s, 100% of 2-year-old children in The Netherlands[11] and two thirds of 4-year-olds in Tennessee[12] had documentation of antibodies to *P. carinii*. Infection in the AIDS patient is postulated to be an induction of dormant organisms or an inability to suppress the organisms upon re-exposure. Both of these mechanisms reflect the immunologic compromise of HIV infection.[4]

Once inside host lungs, *P. carinii* adheres to type-I alveolar cells, develops into cysts, and produces trophozoites that are released when the pneumocytes burst.[4] Progression of infection produces consolidation of the alveoli as the trophozoites proliferate, inflammatory cells congregate, and alveolar cells are destroyed.[13]

In patients with *P. carinii* pneumonia without HIV infection, symptoms typically tend to be much more severe, with tachypnea in most cases.[14] Symptoms of *P. carinii* pneumonia in HIV-infected patients may be subtle or may include chest or sternal discomfort, nonproductive cough, dyspnea on exertion, and fever. Patients may even present with symptoms consistent with acute asthma, confounding the diagnosis of *P. carinii* pneumonia,[15] and 50% of patients have a normal physical examination on presentation.[4] Some AIDS patients subsequently diagnosed with *P. carinii* pneumonia have presented with pneumothoraces.[16-19] In these cases, there had been no prior trauma to the lungs, such as might occur with mechanical ventilation or transbronchial biopsy.

When examined histologically, *P. carinii*-infected pulmonary tissue typically shows interstitial thickening due to hyperplasia and hypertrophy of type-II pneumocytes and infiltration of lymphocytes and plasma cells.[20] As described, the alveoli are usually filled with a proteinaceous exudate. In addition, there may be evidence of tissue destruction in the form of cysts, cavitations, bullae (where the intra-alveolar septae have been destroyed), and subpleural emphysematous blebs.[17,21] In some cases, *P. carinii* affects the vasculature by obliterating vessel walls. The results of progressive infection are ventilation-perfusion mismatching, oxygenation defects, and reduced pulmonary compliance.[22] In addition, Travis et al[21] found interstitial fibrosis in 63% of the cases they examined.

Many diseases are clinically indistinguishable from *P. carinii* pneumonia, and some may actually occur as co-infections. These pneumonias may be caused by bacteria such as *Streptococcus pneumoniae, Hemophilus influenzae, Staphylococcus aureus*, and *Mycobacterium* species; the fungi, *Cryptococcus neoformans* and *Histoplasma capsulatum*; the parasites, *Toxoplasma gondii* and *Strongyloides stercoralis*; and viruses such as herpes simplex, cytomegalovirus, and adenoviruses. In addition, Kaposi's sarcoma or lymphoma; drug toxicity; and, particularly in children, lymphocytic interstitial pneumonitis may be observed in HIV-infected patients in association with *P. carinii*.

Mycobacterial Infection

From 1953 to 1984, *Mycobacterium tuberculosis* infections declined about 5% per year in the United States. In 1986, however, this trend reversed, and tuberculosis cases increased by 2-6%.[23] From 1984 to 1990, there were about 28,000 more cases than expected, and the largest increases in incidence occurred in areas with the largest HIV-infected population.[24] Data indicate that the general population in the United States demonstrates a 0.1% prevalence of active disease, whereas among the HIV-infected, the prevalence is 3.8%.[25]

The HIV-infected groups who are most vulnerable to infection with *M. tuberculosis* are blacks from Africa, Hispanics, Haitians, and intravenous drug users.[26,27] Additionally, data support a greater trend for active disease in those who exhibit positive-purified-protein-derivative (PPD) reactions (a positive tuberculin skin test) and HIV seropositivity or who later become HIV-infected.[28,29] It is important to note that the air-

borne transmission of tuberculosis renders the entire HIV population susceptible. Moreover, because of its greater virulence, *M. tuberculosis* may cause disease earlier in the course of HIV infection than *P. carinii*, if the $CD4^+$ lymphocyte count is used as a marker of disease progression.[30]

M. tuberculosis appears to cause active disease in two distinct ways.[31] The alterations in cell-mediated immunity render the host vulnerable to latent reactivation of *M. tuberculosis* infection, and new exposures that progress to active infection may also occur. It is possible that the growing incidence of tuberculosis in prisons, homeless shelters, and hospitals is attributable to the increased incidence of HIV infection.[26]

HIV-infected persons with tuberculosis present with fever, cough, and pulmonary infiltrates, but the chest radiographic presentation may not be consistent with the presentation of tuberculosis in the non-HIV-infected population.[29,31,32] Furthermore, some extrapulmonary manifestations of tuberculosis may be more commonly observed: brain abscesses and meningitis,[33-35] pericarditis,[35,36] pleural effusions,[37,38] and mycobacteremia in 40% of cases.[39]

Several other species of mycobacteria may cause disease in these patients. *Mycobacterium avium-intracellulare* complex (MAC) produces systemic bacterial infection most often.[39] Up to 33% of HIV-infected patients are diagnosed with MAC bacteremia before death, and more than 60% have the diagnosis established at autopsy. This opportunistic pathogen resides in water and soil, and usually gains access to the host through either the respiratory or gastrointestinal tracts.[40] Symptoms are nonspecific and may include fever, weight loss, and crampy diarrhea that may persist for months. Infection with MAC typically has a slowly progressive course.[39,41,42] The other atypical mycobacterial pathogens are *M. chelonei, M. fortuitum, M. gordonae, M. haemophilum, M. kansasii, M. mahmoerse, and M. xenopi*, all of which have a clinical presentation similar to MAC.[39] All of these atypical mycobacteria are frequently cultured from pulmonary specimens, but the significance of this in terms of pulmonary morbidity has not been clearly established.[32]

Community-Acquired Infection

Community-acquired bacterial pathogens may also play a role in HIV disease. Pneumococcal pneumonia occurs with an incidence of 17.6 cases per 1,000 persons with HIV infection compared to the incidence in the general population of only 2.6 cases per 1,000 persons.[43] Recurrences of this infection and of infections with *H. influenzae* are reportedly higher in HIV-infected patients, and bacteremia develops more frequently with both of these pathogens.[44-46] Other bacterial agents commonly causing pneumonia include *Staphylococcus aureus, Branhamella catarrhalis, Legionella pneumophila, and Mycoplasma pneumoniae*. All of these infections produce symptoms characteristic of bacterial pneumonias in the non-HIV-infected subject (ie, fever, productive cough, pleuritic chest pain, and physical signs consistent with pulmonary consolidation). Patients tend to be more acutely symptomatic compared to patients with *P. carinii* pneumonia.[45] *H. influenzae* and *S. pneumoniae* are most frequently responsible for tracheitis in HIV-infected patients,[32] although they also cause bacterial tracheitis in non-HIV-infected patients.

Morbidity secondary to bacterial pathogens is probably the result of both impaired T-cell and B-cell immunities. HIV disease adversely affects humoral immunity by a decreased production of antibodies. Homosexual men with AIDS have been found to demonstrate a decreased response to pneumococcal vaccine when compared with HIV-negative homosexual men.[47] T-cell functional abnormalities include impaired phagocytosis, impaired chemotaxis, and δ-interferon deficiency.[48,49]

Two rare bacterial pathogens that occasionally cause disease are *Nocardia asteroides* and *Rhodococcus equi*. *R. equi* (formerly *Corynebacterium equi*) is an aerobic Gram-positive coccobacillus found originally as the causative pathogen of pneumonia in foals.[50,51] In HIV-infected patients, it is believed that the organism thrives inside phagocytes, and HIV infection has recently become the most important underlying condition for *R. equi* infection. On radiograph, it presents as a unilateral or bilateral cavitary pneumonia, and hemoptysis is also a prominent clinical feature.[51-55] Nocardial pulmonary infections present with pleuritic chest pain in up to one third of cases,[56] and this may be a distinguishing feature of that pathogen.

Viral Infection

Cytomegalovirus (CMV) is probably the most important viral pathogen in HIV disease. Mortality from *P. carinii* pneumonia is 14%; however, this rate increases to 92% when there is concurrent CMV pneumonia.[44] CMV is a herpes virus usually acquired in childhood, at which time it only infrequently causes clinical disease. Because of the immunosuppressive effects of HIV, CMV is often reactivated. It has been estimated that up to 90% of HIV-infected patients will have evidence of CMV infection at autopsy.[57,58]

Making the distinction between CMV infection of the lungs and true CMV pneumonia is difficult.[59] The frequency of CMV pneumonia in HIV-infected patients is not entirely clear. The isolation of CMV from bronchoalveolar lavage fluid may be due to the severity of immunosuppression rather than to actual pneumonia.[60,61] However, systemic disease, including pneumonia and other organ dysfunction such as retinitis or colitis, is quite common in the late stages of HIV infection.

Herpes simplex virus is also capable of producing either a localized or diffuse pneumonitis. When mucocutaneous organisms are reactivated with subsequent aspiration into the tracheobronchial tree, a focal necrotizing process may occur.[62] If viremia ensues, the host may develop a diffuse interstitial pneumonia.

Fungal Infection

Cryptococcus neoformans is probably the most common pulmonary fungal pathogen in HIV disease, occurring as a primary manifestation in 5% of HIV-infected patients.[63] The organism is present in the excreta of pigeons and chickens and is easily inhaled into the peripheral airways. Meningitis is the most common presentation (70-85%); concurrent pneumonia occurs in 30% of patients with meningitis.[63,64] A persistent fever is present in 60-70% of cases, and pleuritic chest pain is common.[65]

Histoplasma capsulatum is spread via the droppings of birds and bats, and in its endemic areas the majority of the population has been exposed through inhalation.[66] Histoplasmosis can be a disseminated disease in up to 4-5% of HIV-infected patients living in endemic areas, and in half of these, primary pulmonary histoplasmosis is the first manifestation of AIDS.[67,68] Symptoms are fairly typical and may include pleuritic chest pain.

Coccidioides immitis is endemic to the southwestern United States. In Tucson, Arizona, *C. immitis* is responsible for 50,000 new infections per year.[69] In patients with immunodeficiency, the disease may be disseminated and life-threatening.[70] Symptoms are typical, and infections usually occur when the $CD4^+$ lymphocyte count is less than $150/mm^3$.[70]

Saccharomyces cerevisiae (common brewer's yeast) has been reported to cause pulmonary infection in AIDS.[71] The organism produces pulmonary histopathologic changes including hyaline membranes, alveolar septal damage, and bronchial cell hyperplasia.[71] Pulmonary aspergillosis is likewise destructive to the lungs and may cause an obstructing, invasive bronchitis as well as pneumonitis.[72,73] Pulmonary infection with *Aspergillus* species carries a very high mortality. Finally, *Candida* species, although rarely a primary pulmonary pathogen, have potential for life-threatening disease, such as esophagitis and fungemia, as well as tracheobronchitis.[74]

Parasitic Infection

Strongyloides stercoralis is a parasite endemic to tropical and subtropical areas. When *S. stercoralis* causes pulmonary morbidity, infection is typically a late sign of multiorgan involvement.[75] The lung is the most common extraintestinal organ involved, and when the lung is infected, the worm induces a necrotizing bronchopneumonia.[76] Clinical signs of disease include dyspnea, cough, wheezing, and hemoptysis. Airway constriction is probably the result of larva-induced bronchial hyperreactivity or mediators released from eosinophils.[76] One of the most unusual aspects of this disease is the latency of infectious symptoms. The organism may be harbored in the gut for decades before immunologic compromise leads to morbidity.[75] Mortality from this disease has been estimated at 86%.[77] Another protozoan, *Toxoplasma gondii*, may also cause a necrotizing process in the lungs[78] and may occasionally cause pharyngitis.[79]

Malignancy

Two primary malignancies cause important pulmonary morbidity. Kaposi's sarcoma manifests most commonly as pink, red, or violet lesions of the skin. The lesions are frequently located on the head, neck, trunk, or extremities, and on the mucous membranes of the gingiva, tonsils, and palate.[80] Although one third of the patients originally identified with AIDS had Kaposi's sarcoma as the only manifestation of disease, by 1987 only about 10% of patients were noted to have Kaposi's sarcoma as the primary indicator of AIDS.[81] Of those with both HIV infection and Kaposi's sarcoma, 20-40% manifest signs of pulmonary involvement due to Kaposi's sarcoma.[82,83] Risk factors for the disease are not well established but may include concurrent infection with cytomegalovirus or another virus and the use of nitrite inhalational vapors.[80]

Patients with Kaposi's sarcoma in association with dyspnea, fever, dry cough, hemoptysis, and/or hypoxemia should be evaluated for pulmonary Kaposi's sarcoma.[80] However, pulmonary involvement may occur in the absence of skin lesions. In addition, hoarseness may occur if there are lesions on the vocal cords. Endobronchial or laryngotracheal lesions may cause wheezing or stridor. If lesions obstruct the lymphatic system, a pleural effusion may develop, and the patient may have concomitant pleuritic chest pain.[84]

The prognosis for pulmonary Kaposi's sarcoma is poor, with life expectancy averaging from 2-15 months.[80,84] Death is often due to concurrent infections or to airway obstruction, pulmonary hemorrhage, or massive pleural effusions caused by Kaposi's sarcoma.

The other major HIV-associated malignancy is non-Hodgkin's lymphoma. Its incidence in the HIV-infected population is 60 times greater than in the general population.[85] When found in an HIV-positive person, non-Hodgkin's lymphoma is diagnostic for AIDS.[1] The Epstein-Barr virus (EBV) has been postulated to be a causative agent of this B-cell lymphocyte malignancy.[86,87] The overall incidence of this malignancy in the lungs is unknown, but pulmonary symptoms may be the only manifestation of lymphoma.[88] Most often, however, patients present with disseminated lymphoma affecting the gastrointestinal tract, central nervous system, and liver. Median survival after diagnosis of pulmonary lymphoma is 6 months.[4]

Inflammatory Disease

Like other immunocompromised patients, such as bone-marrow or organ-transplant recipients, those with AIDS may develop an idiopathic inflammatory process in the lungs. Three of these processes have been described in the literature. Lymphocytic interstitial pneumonitis (LIP) most commonly oc-

curs in children. A second process, nonspecific interstitial pneumonitis, has been diagnosed in 11-38% of AIDS patients with pulmonary symptoms.[44,89] The disease is characterized by histopathologic evidence of interstitial inflammation with mononuclear cells, typically lymphocytes, in the absence of infection or malignancy. Symptoms are nonspecific, may include mild cough, dyspnea, and fever, and may either persist, progress, or resolve spontaneously.[89] No consistent etiologic agent has been identified, although there is a suggestion that HIV may be responsible.[90]

The third of these inflammatory disorders is the diffuse infiltrative $CD8^+$ lymphocytosis syndrome. This disease occurs most frequently in non-Caucasians.[91] The parotid glands are typically enlarged; adenopathy is apparent throughout the body; the liver and spleen are enlarged; and the lungs show a pattern of interstitial inflammation. Dryness of the mouth is a common symptom.[91]

In addition, several other noninfectious complications have been associated with HIV disease. Pulmonary hypertension may occur leading to abnormalities in gas exchange.[92-96] Polos et al[96] found that the most common pathologic finding associated with pulmonary hypertension was plexogenic arteriopathy. The etiology of this vascular destruction is unclear; however, it may represent another manifestation of an immunologic response to the virus.

Foreign body granulomatosis is an inflammatory process in the lung that occurs in response to antigenic invasion, frequently a solid substance that has been crushed and injected peripherally. Progression of this granulomatous process leads to bullous changes, pulmonary edema, and bronchitis.[97,98] Cocaine injection has the potential to cause chronic bronchitis and hemoptysis,[99] and heroin abuse is associated with pulmonary edema.[100] Other, less common pulmonary complications have been described in the literature, including aspiration pneumonias, lung abscesses, septic thromboemboli, endocarditis, and pulmonary artery aneurysms.[101,102]

Pediatric Pulmonary Disease

Pediatric HIV-infected patients with life-threatening complications are being seen more frequently in intensive care units. Up to one third of children born to HIV-infected mothers demonstrate seropositivity and develop AIDS.[103] The virus can be transmitted through the placenta, during delivery, or through breast milk. Like adults, children are at risk for acquiring HIV infection through transfusions of blood products, although this risk has been greatly reduced through screening of the blood supply.

Clinical features of AIDS in children are similar to those in adults, and include failure to thrive, persistent fevers, lymphadenopathy, respiratory disease and infection, and neurologic abnormalities. The Children's Hospital AIDS Program[104] noted that 68% of children with AIDS had encephalopathy. These are chronic manifestations of HIV disease. However, children with HIV infection are susceptible to acute life-threatening illnesses. In addition to pulmonary opportunistic infections, these include dilated cardiomyopathy and congestive heart failure;[105] arteriopathies of the heart, lungs, kidneys, spleen, intestines, and brain progressing to ruptured aneurysm or infarction;[106] renal disease including glomerulonephritis with hypoalbuminemia, proteinuria, azotemia, and edema;[107] neoplasms of the lungs, brain, and intestines;[108] and thrombocytopenia.

Lymphocytic Interstitial Pneumonitis

One of the most important pulmonary problems in pediatric HIV-infected patients is lymphocytic interstitial pneumonitis (LIP). Of children with so-called vertically acquired HIV (ie, transmitted from a parent), 30-50% develop this disease,[109,110] and in the pediatric population with HIV infection, LIP is an AIDS-defining illness.[2] Usually presenting in the second or third year of life, the disease typically manifests with cough, bronchospasm, and, later, digital clubbing.[111] In the lungs, the interstitium is infiltrated with lymphocytes causing a diffuse thickening that involves the alveolar septa, the interlobular septa, and the subpleural and peribronchial lymphatic channels.[112] Fibrosis is the result. Thus, the patient typically demonstrates both obstructive and restrictive pulmonary mechanics.

The etiology of LIP is not known, but HIV is one explanation.[113,114] Some investigators believe that the EBV acts synergistically with HIV to produce the histopathologic changes of LIP.[115-118] It has been reported that EBV has been recovered from up to 80% of pulmonary histopathologic specimens from patients with LIP.[118]

Other disorders of immune dysfunction may compromise the pulmonary status of children with HIV. Reactive airways disease is common among children with immunodeficiencies, probably as a result of the chronic airway inflammation associated with persistent infection.[118] Lymphoid hypertrophy affecting the tonsils and adenoids may be severe enough to cause obstructive sleep apnea in young children.

Viral Infection

Viruses more common to children may produce significant pulmonary disease. Varicella-zoster virus, the etiologic agent of chicken pox, may be associated with pneumonia. The rate at which respiratory compromise with pneumonia occurs in HIV-infected patients exceeds that of varicella-zoster infections in other immunocompromised hosts.[119] Additionally, the infection recurs often in the pediatric HIV population. The respiratory syncytial virus may also produce a much more severe and protracted course in the HIV-infected host. The measles virus, likewise, may produce a devastating pneumonia, and vaccination against the virus may not confer immunity to these children.[118] With any of these viruses, respiratory fail-

ure oftentimes ensues requiring ventilatory support.

Mycobacterium tuberculosis Infection

Mycobacterium tuberculosis has become a particularly menacing pathogen for HIV-infected children. In large cities, pulmonary tuberculosis has presented in children in epidemic proportions. From 1987 to 1991, the incidence of pulmonary tuberculosis in children increased over 300%,[120] and in the past 2 years, pediatric cases have increased by another 40%.[121] Typically, 60% of childhood tuberculosis occurs in children under 5 years of age.[122,123] HIV-infected children are at risk because they may be living with or may be exposed to adults who are themselves HIV-infected and who have other risk factors for tuberculosis.

Unlike adults, pulmonary tuberculosis in children most often represents a new infection.[121] Children typically do not present with clinical findings suggestive of infectious tuberculosis, eg, fever, cough, and a chest radiograph demonstrating pulmonary infiltrates; instead, variable or self-limited symptoms such as fatigue, anorexia, and skin rash may occur.[121] Enlarged lymph nodes surrounding the tracheobronchial tree may cause symptoms of airway compression and atelectasis or obstructive emphysema. In one study, lymphadenopathy, particularly of the hilar and paratracheal nodes, was found in 92% of pediatric tuberculosis cases.[124] Extrapulmonary tuberculous disease, such as meningitis and joint disease, is more common in children than in adults.[125]

Diagnosis of Pulmonary Pathologic Processes

The key to improved treatment and longer survival from most of these pulmonary pathogens is the rapid verification of a diagnosis. Several diagnostic procedures require the expertise and aid of respiratory care practitioners.

Radiography

The usual initial diagnostic step is the chest radiograph, although, as indicated in Table 1, its utility in establishing a diagnosis is not always readily apparent. Several distinct processes may present similarly on the chest radiograph.

The presentation of *P. carinii* pneumonia is usually insidious. Of patients diagnosed with *P. carinii* pneumonia, 5-10% present with a normal chest radiograph.[126,127] More commonly, however, the infection produces a bilateral interstitial and/or alveolar infiltrative pattern that typically begins in the perihilum and progresses symmetrically towards the periphery of the lungs. In addition, there appear to be two types of cysts noted on radiographs of the *P. carinii*-infected lung: intrapulmonary cysts and subpleural bullous emphysematous blebs.[128] These parenchymal changes can be seen early on computed tomography (CT) scans of the chest.[129] There is considerable potential for rupture of these cysts and blebs; therefore, pneumothoraces are an important clinical threat. Another important radiologic observation is that infection may localize to the upper lobes of the lungs, particularly in pa-

Table 1. Radiographic Patterns in HIV-Associated Pulmonary Disease

Pattern	Disease
Normal Findings	*P.carinii* pneumonia
	Disseminated *Mycobacterium avium*-complex (MAC)
	Disseminated histoplasmosis
	Tuberculosis
	Kaposi's sarcoma
	Nonspecific interstitial pneumonitis
Diffuse reticulonodular infiltration	*P.carinii* pneumonia
	Disseminated tuberculosis
	Disseminated histoplasmosis
	Disseminated coccidioidomycosis
	Lymphocytic interstitial pneumonitis
	Nonspecific interstitial pneumonitis
	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
	Cryptococcosis
	Community-acquired bacterial pneumonia
	Strongyloidosis
	Respiratory syncytial virus pneumonia
	Atypical tuberculosis
	Lymphoma
Focal airspace consolidation	*P. carinii* pneumonia
	Bacterial pneumonia
	Kaposi's sarcoma
	Cryptococcosis
	Legionellosis
	Mycoplasmal pneumonia
	Community-acquired bacterial pneumonia
	Strongyloidosis
Primary upper lobe infiltrates	*P. carinii* pneumonia
	Tuberculosis
	Rhodococcus equi pneumonia
Adenopathy	*P. carinii* pneumonia
	Tuberculosis
	Disseminated MAC
	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
	Cryptococcosis
Pleural effusion	Kaposi's sarcoma
	Tuberculosis
	Cryptococcosis
	Non-Hodgkin's lymphoma
	Histoplasmosis
Cavitations and pneumatoceles	*P. carinii* pneumonia
	Tuberculosis
	Rhodococcus equi pneumonia
	Strongyloidosis
Pneumothorax	*P. carinii* pneumonia

tients receiving aerosolized pentamidine as chemoprophylaxis against *P. carinii*.

The radiographic picture of tuberculosis may be either identical to that of classic tuberculosis of the non-AIDS population or it may be atypical.[37,38,130-132] Those patients who acquire *M. tuberculosis* infections early in the course of HIV may present with more typical chest radiographs showing upper lobe infiltrates with cavitation. Those who become infected during more advanced stages of AIDS typically show diffuse interstitial infiltration with lower lobe involvement, intrathoracic adenopathy, and pleural effusions. Because many patients with advanced immunosuppression are anergic, caution must be applied in assessing skin tests in patients with chest radiographs showing diffuse pulmonary disease; the disease may be tuberculosis despite lack of a positive response to the antigen.

Primary pulmonary tuberculosis of childhood may present with one of four different radiologic patterns: lobar or segmental parenchymal disease, lymphadenopathy, pleural effusions, or miliary involvement.[121] Atelectasis or hyperinflation may be complications of airway compression by enlarged lymph nodes. Pleural effusions are less common in young children than in adolescents. Miliary disease is more common in older children.[121] The chest roentgenogram of the child with pulmonary tuberculosis returns to normal slowly, and hilar adenopathy may be apparent for years.[133]

Although CT of the chest can detect the miliary disease of pulmonary tuberculosis prior to the chest radiograph,[134] the value of the chest CT scan is probably greater in the assessment of HIV-related neoplasms. When the nodules or pleural effusions due to pulmonary Kaposi's sarcoma or non-Hodgkin's lymphoma are small, a CT scan may provide earlier evidence for malignancy than a chest radiograph.[80] Lesions inside or outside the airways causing compression may also be detected by CT scan. If intrathoracic adenopathy is evident, without the diagnosis of Kaposi's sarcoma or lymphoma, then the chest CT may suggest an infectious process (Table 1).[80]

Sputum Analysis

Sputum analysis is another essential step for proper identification of pulmonary pathogens. Although collection of a sputum specimen may seem routine, obtaining a good sample requires diligence. For some infectious agents, a prescribed collection procedure may enhance the diagnostic power of sputum.

The diagnosis of bacterial infections of the lung is made from culture of pulmonary specimens in approximately 50% of cases.[44] When a patient's chest radiograph is free of infiltrates, yet purulent sputum is produced, one should suspect tracheobronchitis due to either a bacterial or fungal pathogen. In most situations, if the patient has an effective cough, a sputum specimen is simply collected in a sterile container and sent for analysis. Occasionally, collection of a good sample requires induction of sputum with an aerosolized hypertonic saline solution.

The diagnosis of pulmonary *M. tuberculosis* in a child is not usually based on the bacteriologic analysis of sputum because specimens are generally difficult to obtain, especially in young children. Instead, gastric aspirates obtained on three consecutive mornings may either confirm or eliminate the diagnosis of pulmonary tuberculosis.[125] However, this procedure has a reported sensitivity of only 30-40%.[123] The diagnosis of pediatric pulmonary tuberculosis is most likely to be based on a careful history of exposure, tuberculin skin-test results, the chest radiograph, and the physical examination.[121]

In patients with suspected *P. carinii* infection, sputum induction becomes essential. Expectorated sputum obtained without the aid of sputum induction from those with *P. carinii* will most often yield negative results, even when special stains are used to detect this organism. As described previously, pneumocystis organisms dwell primarily within alveoli, and, consequently, are not easily expectorated with pulmonary secretions. Thus a proper procedure for sputum induction should be applied in those patients suspected of having *P. carinii* pneumonia. Such a procedure has been described using ultrasonic aerosolization of hypertonic (3%) sodium chloride solution.[135,136] In our institution, an optimal specimen is one that results from a maximal patient effort and a deep cough.[136] Patients are instructed to gargle and to rinse with the 3% solution prior to collecting any sputum in order to minimize oral contaminants in the sample. This method of induction yields positive results in more than 92% of patients not on aerosolized pentamidine chemoprophylaxis.[137] We believe that this procedure should become standard practice for all respiratory care practitioners caring for HIV-infected patients.

Though seemingly benign, sputum induction procedures may be associated with complications. The hypertonicity of the solution coupled with the aerosol volume and particle size may invoke bronchospasm in patients with reactive airways. This is especially true in pediatric patients who have smaller airways and are more likely to develop bronchospasm. Miller et al[138] reported significant arterial desaturation that persisted for 20 minutes after the procedure. This desaturation was attributed to ventilation-perfusion mismatch; however, it could not be predicted from patients' baseline arterial saturation, chest radiographs, or alveolar-arterial oxygen gradients. Close monitoring of patients undergoing sputum induction is recommended.

Bronchoscopy

If sputum induction fails to yield a specimen, if the specimen is negative for *P. carinii*, or if the procedure could not be performed adequately, then fiberoptic bronchoscopy should be considered as the next diagnostic procedure. Respiratory care practitioners often assist with the procedure as well as ad-

minister supplemental oxygen to patients during the procedure. Bronchoscopy may be performed solely to visualize the airways. However, the procedure is most often performed to obtain pulmonary specimens. Lavage of the bronchial tree with normal saline (bronchoalveolar lavage, or BAL) yields an aspirate of fluid, which is analyzed for pathogens. The organisms for which BAL is particularly useful include most bacteria, fungi, viruses, and especially *Pneumocystis* species. The diagnostic yield for *P. carinii* with a BAL procedure ranges from 84-97%.[139-141] Occasionally, a histopathological specimen is required for the accurate diagnosis of these opportunistic pathogens. A biopsy forceps is inserted through the bronchoscope and is used to obtain samples of endobronchial or pulmonary parenchymal tissue. The biopsy procedure is associated with an incidence of pneumothorax ranging from 1-9%.[4]

BAL has been performed recently without the aid of a bronchoscope, using a specially developed catheter. In a study of 28 patients suspected of having *P. carinii* pneumonia, Bustamante and Levy showed a superiority of yield of catheter BAL over sputum induction for diagnosing *P. carinii*.[142] The authors also reported less cough with the catheter as compared to sputum induction, greater cost-effectiveness, and easier performance of the procedure, allowing nonpulmonary and nonphysician personnel to obtain BAL specimens.[142] Additional clinical trials are needed before the use of the catheter for lavage becomes routine.

Airway appearance may be assessed with the bronchoscope. Kaposi's sarcoma lesions may be visualized by their characteristic appearance. If no such lesions are seen, however, BAL cannot establish the diagnosis of pulmonary Kaposi's sarcoma. Occasionally, a diagnosis can be made from endobronchial biopsies.[143,144] However, biopsies of Kaposi's lesions in the lung may cause hemorrhage leading to compromise of the airway. Parenchymal lesions of Kaposi's sarcoma are even more difficult to diagnose. Definitive diagnosis is usually based on characteristic histology from a large piece of tissue obtained at open-lung biopsy, or most often, at autopsy.[82,144-146] The role of bronchoscopy and transbronchial biopsy for establishing the diagnosis of non-Hodgkin's lymphoma is similar to that for Kaposi's sarcoma.

LIP may be presumptively diagnosed from BAL results. Lavage specimens may demonstrate an overabundance of white blood cells, particularly $CD8^+$ lymphocytes.[147] The diagnosis is typically established after a transbronchial or an open-lung biopsy. Current clinical practice recommends that open-lung biopsy be limited to patients with progressive pulmonary disease and nondiagnostic BAL who are not candidates for transbronchial biopsy.[14] This includes patients with bleeding disorders or refractory hypoxemia. In addition, patients suspected of having multiple disease processes and who are not improving on current therapy may be candidates for open-lung biopsy. However, because of its morbidity, and because most diagnoses can be established by bronchoscopy, open-lung biopsy has limited diagnostic utility.

Tests of Pulmonary Function

Although not useful for diagnosis, pulmonary function testing is sometimes useful in determining the severity of pulmonary disease or the need for follow-up diagnostic procedures. Spirometry measurements demonstrated an important decrease (less than 80% of predicted) in total lung capacity and vital capacity in AIDS patients with pulmonary disease, in a report by Stover et al.[148]

P. carinii pneumonia was the diagnosis most often responsible for the changes. Expiratory flowrates (as reflected by the FEV_1/FVC) increased beyond the 80%-normal value in those patients with *P. carinii* pneumonia.[149-151] This finding was postulated to be due to increased elastic recoil secondary to interstitial lung disease. Conversely, in one study, 21% of those with *P. carinii* pneumonia and 42% of those with other diseases demonstrated airflow obstruction as manifested by a $FEV_1/FVC < 75\%$.[150]

In this same study, all patients with endobronchial Kaposi's sarcoma demonstrated airflow obstruction. In such patients, the combination of peribronchiolar lesions and large tumors at bifurcations of the major airways is probably responsible for clinically important obstruction.[148] However, other patients with no evidence of endobronchial masses demonstrate low FEV_1/FVC. An immunologic etiology has been postulated for the ventilatory obstruction: reactive airways may occur due to high levels of circulating immunoglobulins, such as IgE, or to local deposition of immune complexes.[152]

The single-breath measurement of diffusing capacity (D_{LCO}) has proven to be a highly sensitive test for the detection of *P. carinii* pneumonia.[44,149,153,154] The D_{LCO} was less than 80% of predicted in 89-100% of patients with documented *P. carinii*. The test has been used as an adjunctive, noninvasive tool for the evaluation of HIV-infected patients who have a persistent cough but normal chest roentgenograms and normal arterial blood-gas values. This decreased diffusion is attributed to the thickening of the alveolar-capillary membrane caused by the attachment of *P. carinii* trophozoites to the epithelium.[148] Diffusion capacity improved after successful treatment of *P. carinii* pneumonia, leading investigators to conclude that fewer intra-alveolar parasites produced a thinner alveolar-capillary membrane.[155] Although it is a sensitive technique, the test is not specific. Both HIV-negative intravenous drug abusers and patients with pulmonary parenchymal Kaposi's sarcoma may demonstrate low diffusion capacities.[156]

Sophisticated assessments of oxygenation may be performed when pulmonary disease is suspected. Hypoxemia at rest occurs often; however, it is an unreliable predictor of the presence of disease. Stover and Meduri[148] reported that although 64% of AIDS patients with pulmonary symptoms had an abnormal alveolar-arterial oxygen difference [$P_{(A-a)O_2}$] for oxygen at rest, 91% exhibited a greater than normal difference after 1.5 minutes of exercise on a 2-step staircase.[148] Moreover, in patients with *P. carinii* pneumonia, the $P_{(A-a)O_2}$ was

frequently abnormal despite a normal chest roentgenogram. Increases in ventilation-perfusion mismatch are the most likely explanation for this observation. The specificity of the $P_{(A-a)O_2}$ for *P. carinii* pneumonia is greater than that of the D_{LCO}, and because it requires less technical sophistication, measurement of the $P_{(A-a)O_2}$ gradient may be useful for evaluating patients with normal chest radiographs for *P. carinii* pneumonia. Several other HIV-related pulmonary diseases do not demonstrate abnormal differences, although they can present with a normal chest radiograph (Table 1).

The pulse oximeter can also provide useful information. Smith et al[157] measured arterial saturation by pulse oximetry (S_{pO_2}) in AIDS patients with *P. carinii* pneumonia and found that 85% had an S_{pO_2} of < 90% after exercise. Patients with other pulmonary diagnoses and those recovering from *P. carinii* pneumonia did not demonstrate such findings. Sauleda et al[158] found that transcutaneous oxygen saturation fell by a mean of 4% in patients with *P. carinii* pneumonia after 2 minutes of pedaling on a stretcher bed. Conversely, patients with other causes of pneumonia demonstrated a mean saturation improvement of 2% after pedaling.

Laboratory Tests

As already noted, leukopenia may result from HIV infection. As patients become more lymphocytopenic, opportunistic infections and other diseases may become more prevalent. Conversely, in those with LIP or other lymphoproliferative diseases, $CD8^+$ lymphocyte counts are elevated, and polyclonal hypergammaglobulinemia predominates.[112] Thrombocytopenia (< 100,000 platelets/mm^3 blood) may also be noted as the disease progresses.

In patients with *P. carinii* pneumonia, measurement of the serum lactate dehydrogenase (LDH) level may be helpful. LDH, the enzyme that catalyzes the interconversion of lactate and pyruvate, is liberated from injured lung tissue. In one series, only 7% of patients with *P. carinii* pneumonia had normal LDH levels at diagnosis.[159] An LDH level of > 225 IU/L coupled with an increase in $P_{(A-a)O_2}$ of > 10 torr after exercise yield a 97% specificity for the diagnosis of *P. carinii* pneumonia.[160] However, elevations of LDH may be seen in other diseases that cause lung injury.

Another important diagnostic tool is the tuberculin skin test. Because the ability to respond to an intradermally placed antigen is dependent on cell-mediated immunity, HIV-infected individuals may exhibit no reactivity in the late stages of disease. Studies estimate that only about 40% of HIV-infected patients with tuberculosis have positive PPD tests for tuberculosis.[31] As a consequence, this may be a serious issue for infection control as well as for patient and health-worker safety.

Management

One of the goals in the medical management of the HIV-infected patient is the preservation of quality of life for as long as possible. Treatment objectives include: (1) delay of the progression of immune deficiency and improvements in immune compromise; (2) prevention of opportunistic infections; and (3) early diagnosis and treatment of the complications of immune deficiency.[161] Many of these treatment objectives have implications for the respiratory care practitioner.

Pneumocystis carinii Pneumonia

Therapeutic regimens for the treatment and prophylaxis of pneumocystis infections include single-drug therapy or combinations of the following: trimethoprim, sulfamethoxazole, dapsone, clindamycin, primaquine, atovaquone, trimetrexate, intravenous pentamidine, and aerosolized pentamidine.[162] The present standard of care for treatment of *P. carinii* infection is the combination of trimethoprim and sulfamethoxazole for patients who do not have a sensitivity to these agents. The other antimicrobial agents have the potential for significant toxicity. Parenteral pentamidine can produce hypotension, alterations in glucose metabolism that may lead to diabetes, hemolytic anemia, thrombocytopenia, leukopenia, hepatic and renal dysfunction, pancreatitis, ventricular tachycardia, and the Stevens-Johnson syndrome.[163,164] Up to 40% of patients who have received systemic pentamidine have subsequently developed renal toxicity, glucose imbalances, or pancreatitis.[165]

The sulfonamides, dapsone and sulfamethoxazole, may cause hematologic disorders, including methemoglobinemia, hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia, and aplastic anemia. In addition, they may cause peripheral neuropathy, hepatitis, pancreatitis, renal failure, toxic epidermal necrolysis, and allergic myocarditis. Medina et al[166] reported severe methemoglobinemia in 20% of patients receiving dapsone therapy. Primaquine, clindamycin, and trimetrexate may also be responsible for blood disorders. One of the newer antipneumocystis agents, atovaquone, may cause a rash in some patients, but it does not seem to produce bone marrow suppression.[167]

In addition to antimicrobial agents, glucocorticosteroids are advocated for the management of severe *P. carinii* pneumonia to help treat the pulmonary inflammation. For rapidly progressive infections, early use of steroids has been associated with increased survival and more rapid improvements in pulmonary function.[168]

Nebulized pentamidine alone is not indicated for the treatment of acute pneumocystis infections. Current practice recommends its use for prophylaxis but not as first-line therapy. Because of alveolar filling with pneumocystis organisms, the drug may not reach some infected areas of the lung.[169] Similarly, because it fails to reach therapeutic levels in the blood, aerosolized pentamidine is not effective against extrapulmonary disease. It does, however, have a role in the prevention of reinfection of a susceptible patient with *P. carinii*. It is postu-

lated that patients who have multiple *P. carinii* infections have never had the organism completely eradicated, and thus a good chemoprophylaxis regimen is necessary.[170]

In 1989, the U.S. Public Health Service[171] established guidelines for the use of aerosolized pentamidine in HIV-positive patients. For those patients with a known sulfa intolerance and a previous episode of pneumocystis infection, aerosolized pentamidine should be instituted as secondary prophylaxis regardless of $CD4^+$ counts. Primary prophylaxis should be instituted for anyone with a $CD4^+$ count of $< 200/mm^3$. A recent multicenter trial found a smaller risk of pneumocystis infections among those patients receiving aerosolized pentamidine prophylaxis who had a $CD4^+$ count of at least $100/mm^3$ as compared to all other patients receiving prophylaxis with fewer than 200 $CD4^+$ cells/mm^3.[172]

What further defines the effectiveness of these treatments? What role can the respiratory care practitioner play in effecting better treatment outcomes? Because delivery of a drug to the lungs depends on nebulizer design and on the concentration of the solution, several studies have compared types and brands of nebulizers as well as varied dosing regimens to determine which nebulizer-dose combination yields the greatest benefit for pentamidine chemoprophylaxis.[173-181] Based on these studies, the current United States standard for pentamidine prophylaxis is the nebulization of 300 mg of pentamidine isethionate suspended in 6 mL of sterile water via the Respirgard II nebulizer (Marquest Medical Products, Englewood CO) administered once monthly. In Canada and in some European countries, however, an alternative approach is utilized. Rather than a jet nebulizer, the Fisoneb (Fisons, Rochester NY), a hand-held, patient-triggered ultrasonic nebulizer, is used to administer 60 mg of pentamidine every 2 weeks. The smaller and more consistent particle size generated by an ultrasonic nebulizer may ensure greater deposition and better distribution of the drug. Additionally, some feel it is better suited for use at home because it is not gas powered and is reusable.

Several issues further complicate the determination of an optimal treatment method. It is difficult to prescribe aerosolized pentamidine as primary prophylaxis when particle size, delivery method, total dose, and nebulizer efficiency are not standardized. These variables also may be patient dependent. Thus, the occurrence of a good and bad treatment cannot always be predicted. For example, the breathing pattern greatly affects particle deposition and may contribute to some of the complications associated with aerosolized pentamidine therapy. The coordination of the phases of inspiration and expiration, especially inspiration through a mouthpiece and one-way valve, requires a level of comprehension and skill that some younger patients may lack. The bad taste of the drug and the length of each aerosolization therapy may also contribute to poor compliance. Therefore, it is important that practitioners carefully instruct and closely monitor all patients during treatment.

Adverse reactions are associated with aerosolized pentamidine. Complaints include increased salivation, unpleasant taste, nausea, and rash.[183] As many as 90% of patients experience a cough or some form of airway irritation, such as sore throat or bronchoconstriction.[184] Airway irritability may be caused by sulfides in the isethionate, the sterile water diluent, the pH of the solution, and/or the nebulized particle size, such that larger particles delivered to large airways activate the cough mechanism.[185] For patients with hypersensitive airways, pretreatment with a bronchodilator may minimize bronchoconstriction.[186] McSharry et al[187] studied the spirometric changes in patients who complained of bronchospasm with aerosolized pentamidine before and after β-agonist administration. Bronchodilator prophylaxis eliminated the reductions in FEV_1 as well as symptoms in these patients. An additional benefit of bronchodilator prophylaxis may be improved drug delivery to distal airways. In our institution, inhaled albuterol delivered via a metered dose inhaler prior to aerosolized pentamidine has become the standard for those patients who have documented airway hyperreactivity after the administration of aerosolized pentamidine, as well as for patients with reactive airways disease.

Additional adverse pulmonary effects of aerosolized pentamidine include crystallization of the drug,[188] activation of a granulomatous process,[189] and apical bullous changes and accelerated emphysema.[190] There are also reports of spontaneous pneumothorax during aerosolized pentamidine treatments[18,19] and pulmonary hemorrhage occurring in relation to bronchoalveolar lavage.[191] An exception was the report of Camus et al[192] who did not find changes in pulmonary functions in patients prophylactically treated with aerosolized pentamidine compared to patients treated with dapsone, over a 2-year period. Other effects associated with more frequent administration include pancreatitis and hypoglycemia[180] and extrapulmonary pneumocystosis.[193] Finally, aerosolized pentamidine contributes to the difficulty of diagnosing *P. carinii* in those receiving the drug as chemoprophylaxis. The uncharacteristic presentation of *P. carinii* pneumonia in just the upper lobes is well documented.[21,194-196] This is attributed to the poorer apical distribution of aerosolized medications. Chronic aerosolized pentamidine reduces the diagnostic yield from induced sputum and BAL[195] for *P. carinii*.

A United States Public Health Service Task Force and another more-recent multicenter trial suggest that trimethoprim-sulfamethoxazole is superior to aerosolized pentamidine in preventing recurrences of *P. carinii* pneumonia.[172,197] However, 17% of the patients in these clinical trials discontinued sulfa prophylaxis because of severe side effects. Only 3.5% of the patients discontinued pentamidine prophylaxis. Recently, Cheung et al[198] retrospectively studied intramuscular pentamidine for prophylaxis against *P. carinii*. This may be an effective alternative for patients who do not tolerate either trimethoprim-sulfamethoxazole or aerosolized pentamidine. Fallat et al[199] investigated metered-dose-inhaler delivery of pentamidine and concluded that pentamidine levels in BAL fluid were signif-

icantly elevated over levels when the drug is delivered via the Respirgard II nebulizer. Finally, the aerosolization of recombinant interferon δ for treatment of severe *P. carinii* pneumonia is being studied by Sattler et al.[200]

Tuberculosis

Since the beginning of the AIDS epidemic, multidrug-resistant tuberculosis has become more prevalent. In addition, adverse reactions to antituberculous drugs are more frequent in the HIV population. In one study, 18% of patients receiving rifampin for their pulmonary tuberculosis withdrew from therapy due to side effects.[201] This and other complicating factors have necessitated the development of new therapeutic regimens.

Primary treatment regimens for tuberculosis include combinations of isoniazid, ethambutol, rifampin, and para-aminosalicylic acid. Clinical experience has shown that HIV-associated tuberculosis usually responds to these regimens.[201] However, because there have been reports of treatment failures,[35] the Centers for Disease Control and Prevention recommends a protracted treatment time for anyone with tuberculosis who is HIV positive.[201] Among the more important side effects of these drugs are hepatic dysfunction that may be severe or fatal, renal toxicity, hematologic disturbances, and shock.

Secondary treatment regimens for pulmonary tuberculosis have included the agents: ethionamide, cycloserine, pyrazinamide, viomycin sulfate, and streptomycin. These, too, may cause liver or renal toxicity and problems with hearing and vision. As more effective agents are developed to battle multidrug-resistant tuberculosis, additional complications may manifest.

Other Microbes

Eradication of other pulmonary infectious agents remains difficult. Amphotericin B remains the drug of choice for fungal infections, but its renal toxicity occasionally limits its utility. In addition, the relapse and mortality rates for fungal pneumonias remain high.[4] Treatment for CMV pneumonia does not change outcome, nor does treatment for disseminated *Mycobacterium avium-intracellulare* complex.[4] Acyclovir for symptomatic herpes simplex pneumonitis appears effective, but an effective antiviral therapy for EBV, an agent possibly responsible for lymphocytic interstitial pneumonitis, is not available. Glucocorticosteroids have led to clinical improvements in patients with LIP, however.[111]

The American Academy of Pediatrics recommends aerosolized ribavirin therapy for all HIV-infected patients hospitalized with lower respiratory tract disease due to respiratory syncytial virus (RSV) and for those with RSV who require mechanical ventilation.[203] The procedure for aerosolization of ribavirin to treat bronchiolitis resulting from RSV was originally described by Taber et al.[204] However, controversy regarding the efficacy of aerosolized ribavirin for RSV infection continues.

Neoplastic Disease

Treatment for neoplastic diseases of the airways or lungs, eg, Kaposi's sarcoma or non-Hodgkin's lymphoma, is only palliative at this time. Tracheotomy may be required for relief of an airway obstruction due to tumor or hemorrhage.[32] Chemotherapy or radiation therapy are used primarily to relieve symptoms and have been associated with prolongation of life.

Several chemotherapeutic agents should be of particular interest to respiratory care practitioners because of their potential pulmonary toxicity. One of the most important of these is bleomycin. Because of its pulmonary cytotoxic effects, special considerations are necessary in caring for patients who have received bleomycin. The primary pulmonary effects of bleomycin on lung tissue include the development of hyaline membranes, bleb formation in the endothelium of alveolar capillaries resulting in interstitial edema, and proliferation of Type-II pneumocytes with migration into the alveoli.[205] The result is irreversible pulmonary fibrosis characterized by decreased lung compliance and restrictive lung disease. The incidence of clinically important bleomycin pulmonary toxicity is 10% with a mortality of 1%.[205] Early signs of bleomycin toxicity include a nonproductive cough and exertional dyspnea that may progress to respiratory distress, fever, and cyanosis. The chest roentgenogram is characterized by bibasilar interstitial infiltrates early and lobar consolidation later. Hypoxemia is usually noted.[205]

Pulmonary function tests may be more sensitive than physical findings for the toxic effects. Decreases in the D_{LCO} and in the forced vital capacity may precede clinically detectable pulmonary toxicity.[205] For this reason, pulmonary function is evaluated at regular intervals in order to assess for early evidence of bleomycin toxicity.

Oxygen must be administered with caution to these patients as it may potentiate the effects of bleomycin toxicity in the lungs.[205] Postoperative patients who have received bleomycin are especially at risk for pulmonary toxicity at oxygen concentrations not normally thought to be particularly toxic.[205] Other chemotherapeutic agents commonly associated with pulmonary toxicity include mitomycin, carmustine (BCNU), cytosine arabinoside (ara-C), interleukin-2, and methotrexate.[206]

Respiratory Failure

When acute infections progress to respiratory failure, making the decision to support the patient with mechanical ventilation is difficult. The initial reports from the early 1980s documented up to 100% mortality from *P. carinii* pneumonia after the initiation of mechanical ventilation.[207] More recent literature has shown some improvement in mortality despite ventilatory failure.[208-210] A contributing factor to this improvement in survival may be the more discreet use of

mechanical ventilation. Beginning in 1986, criteria were set forth at San Francisco General Hospital to help differentiate those patients who would be intubated from those who would not. Criteria for mechanical ventilatory support included: patients who were experiencing their first episode of *P. carinii* pneumonia, those patients in whom deterioration was preceded by an invasive procedure such as bronchoscopy, patients with a rapid clinical deterioration that occurred prior to diagnosis, patients who specifically expressed a desire to be intubated, and those who had advance directives in place indicating that desire.[210] Prognosis also seemed more predictable. El-Sadr et al[208] differentiated survivors from nonsurvivors. Survivors were those who (1) were battling their first infection of *P. carinii*, (2) had a shorter duration of symptoms, (3) were less hypoxic, (4) required mechanical ventilation just 1-2 days after bronchoscopy precipitated respiratory failure, and (5) demonstrated rapid improvement in P_{aO_2} after mechanical ventilation was initiated.

More recently, noninvasive support of oxygenation and ventilation has demonstrated some success. Miller and Semple[211] applied continuous positive airway pressure, via nasal or face mask, to those in acute respiratory failure from *P. carinii* infection. The use of noninvasive ventilation may be important —by allowing time for ethical discussions with the patient concerning life-support measures.[212] Although the use of positive end-expiratory pressure (PEEP) may be beneficial, PEEP should be applied with caution because of the baseline high incidence of pneumothorax associated with the disease process, and the possible aggravation or precipitation of barotrauma by high pressures.[213]

Surgical Intervention

When a persistent air leak complicates the medical management of patients with *P. carinii*, surgical intervention may be beneficial. Two groups have reported an increased stability of pulmonary status after resections of large bullae[18] or surgical closure with sutures or staples.[214] Asboe et al[215] have recommended *early* surgical intervention in successful management of recurrent pulmonary air leaks.

Minimizing Occupational Risk

Human Immunodeficiency Virus

Respiratory care practitioners face frequent occupational risks when caring for HIV-infected patients. Among the more important threats are exposure to HIV, exposure to aerosolized microbes, and exposure to potentially toxic therapeutic agents and safety devices. Although the major threat is direct contact with the blood of HIV-infected individuals, the virus has been recovered from semen, cervicovaginal fluid, saliva, bronchoalveolar lavage, tears, cerebrospinal fluid, and breast milk.[216] In 1987, the Centers for Disease Control published recommendations for the prevention of HIV transmission to health-care workers.[217] These recommendations are considered part of Universal Precautions and are now the standard of care for all patients.

In an effort to assess the risk to health-care workers of contracting HIV infection through patient care, the Centers for Disease Control and Prevention (CDC) has a voluntary surveillance program for employees of United States health-care facilities. Since the Needlestick Surveillance Study's inception in 1983, the HIV seroconversion rate for those who sustained percutaneous exposure to HIV-infected blood is only 0.36%, or 4 of 1,103 workers enrolled in the program.[218] Workers who reported only mucous membrane or skin contacts had no conversions. British and Canadian studies conducted prior to Universal Precautions showed no seroconversions after either type of exposure.[219,220] Thus, the risk of occupationally acquired HIV is small, and is significantly less than the risk of acquiring hepatitis-B virus infection. One health-care worker who suffered an accidental needlestick from an HIV-infected patient who also had the hepatitis-B virus subsequently contracted hepatitis B but not HIV.[221,222] Studies conducted in the 1970s and 1980s have demonstrated that the overall transmission rate of hepatitis B after a parenteral exposure is 12%.[216]

If accidental exposure occurs, the respiratory care practitioner should be tested at that time for the serologic presence of HIV antibodies. Because most people seroconvert in the first 6 to 12 weeks following exposure, acute symptoms of fever, rash, and lymphoadenopathy during the first 12 weeks must be reported, and serologic testing repeated.[216] In some centers, zidovudine prophylaxis is initiated at the time of significant exposure in an effort to minimize the risk of seroconversion. However, in 1990, the U.S. Public Health Service issued a statement that neither supported nor refuted chemoprophylaxis with zidovudine for occupational exposure to HIV.[222] The CDC reported eight instances of chemoprophylaxis failure, including one in which the HIV strain was zidovudine-sensitive, in its more recent surveillance study.[218] The zidovudine regimen was discontinued or the dose reduced due to adverse symptoms in 31% of health-care workers, 12% missing work for 1 to 49 days due to the symptoms.[218] Two other drugs, zalcetabine (ddC) and didanosine (ddI) are being advocated for HIV prophylaxis in health-care workers after significant exposure, but information about their efficacy and toxicity is not yet available.[223]

In 1991, in an effort to protect patients from potential HIV exposure, the CDC published recommendations to limit the performance of invasive procedures by HIV-positive health-care workers.[224] The recommendations were published after reports of an HIV-infected dentist who allegedly infected five patients. Despite the possible evidence in that case, chart reviews of several thousand patients treated by other HIV-infected health-care workers have failed to reveal a single transmission.[225,226] The 1991 recommendations remain controversial.

Cytomegalovirus

The high incidence of CMV infection among AIDS patients warrants a discussion of exposure risk to respiratory care practitioners. Like HIV, CMV is carried in the blood, semen, tears, saliva, breast milk, vaginal secretions, and cerebrospinal fluid of infected persons.[216] The greatest risk of infection is to the unborn babies of pregnant health-care workers. Fetuses exposed to CMV during the first half of gestation are at risk of developing CMV-related birth defects. Healthy, non-HIV-infected individuals who contract CMV develop a nonspecific, mild, flu-like illness that is self-limited, but they remain asymptomatic carriers of the virus. Adherence to Universal Precautions provides adequate protection to health-care workers from CMV infection.[216]

Tuberculosis

M. tuberculosis exposure is one of the greatest risks for respiratory care practitioners caring for the HIV population. With the HIV-positive population expanding in the inner cities, with the emergence of new strains of multidrug-resistant tuberculosis, and with the performance of crucial cough-provoking tasks related to the diagnosis and treatment of tuberculosis, respiratory care practitioners are particularly at risk for nosocomial transmission. In 1989, in a Florida health clinic, 30 health-care workers who were previously PPD negative converted to positive after two patients with unsuspected tuberculosis were treated with aerosolized pentamidine.[227] Several other incidents have necessitated an updated policy for dealing with the new generation of tuberculosis infection. Thus, the CDC published revised guidelines for tuberculosis control in December 1990.[228]

Although it may be difficult in the HIV population, early diagnosis of contagious persons probably represents the most effective means of controlling the nosocomial spread of this disease. Proper isolation precautions and appropriate antimicrobial therapy are essential. In addition, the use of physical barriers to limit contamination and the use of methods for procedural containment of microbes are necessary. Finally, an aggressive program of transmission surveillance and treatment for health-care workers is vital.

What specific relevance do these goals have for the respiratory care practitioner? Because the emergency room or clinic is usually the site of initial entry into the health-care system for patients with active tuberculosis, respiratory care practitioners who work in these areas should be aware of the signs of active disease. Any persistent, productive cough that is of longer than 3-weeks duration should be considered suspicious for tuberculosis, especially when accompanied by weight loss, fever, anorexia, and fatigue.[228] When a cough is productive, patients are most contagious, and they must be instructed to cover all coughs and sneezes with tissues. This simple method contains most aerosolized particles before evaporation occurs. Persons identified as being potential transmitters of tuberculosis should be removed from common waiting areas. It may even be appropriate for such patients to use surgical masks or valveless particulate respirators until proper isolation can be achieved. We believe that respiratory care practitioners must be unwavering in their use of particulate respirators and committed to assuring that adequate inventories of masks are maintained in all areas of the health-care facility or home-care setting where exposures can occur.

For any procedures involving the provocation of a cough, a patient should be in a negative-flow room or booth equipped with exhaust fans for removal of airborne particles.[228] All procedures related to the diagnosis of suspected pulmonary tuberculosis or to the removal of pulmonary secretions, eg, sputum induction, BAL, tracheal intubation, or suctioning, as well as therapeutic interventions for assisting cough and aerosolized pentamidine treatments, must be performed in such rooms. More specific recommendations for ventilation of acid-fast bacillus isolation rooms have been detailed by the American Society of Heating, Refrigerating, and Air Conditioning Engineers Inc and the Health Resources and Services Administration.[229,230] It is imperative that the doors to such rooms remain closed at all times, and that the close fit of all doors be maintained. Cough-provoking procedures that must be performed in the home should be done in well ventilated areas away from other household members.

In addition to the isolation techniques described, the CDC recommends the use of ultraviolet light as a supplement to ventilation in areas where the risk of transmission is high.[228] Ultraviolet irradiation has germicidal properties, although its efficacy for disinfection of exhaled air has not been proven. Respiratory care practitioners working under ultraviolet lights should be aware of the risks involved. Short-term overexposure can cause keratoconjunctivitis and erythema of the skin, although when the lights are properly used and maintained, the risk is small.[231] Long-term overexposure to ultraviolet light is associated with an increased risk of basal cell carcinoma of the skin and with cataract formation.[232] Ultraviolet lamps are not appropriate for use in small rooms or booths.[228]

Particulate respirators are standard equipment for all health-care workers caring for those with tuberculosis. By design, the masks filter droplet nuclei in the size of aerosolized tuberculous particles. However, wearing them does not guarantee protection from transmission of tuberculosis. Because gaps between the mask and the face create a funnel for air flow, improperly fitted masks provide virtually no protection.[233] It is especially important that respiratory care practitioners be expert wearers of the masks, and that retraining and periodic review of the proper technique for fit of particulate respirators be a priority. Health-care workers with asthma or other airflow limitations may experience difficulty due to the increased work of breathing associated with these masks.

Surveillance of health-care workers at risk for tuberculosis should be ongoing. Respiratory care practitioners who work with the HIV population should have documentation of the PPD skin test prior to employment and should be tested every 6 months.[228] PPD-negative practitioners should also be tested after unprotected exposure to a potentially infectious patient. Chest radiographs are indicated for those who have new reactions > 10 mm or who exhibit symptoms of infection. Practitioners diagnosed with active tuberculous disease should not resume work until drug therapy has suceeded in resolving the cough and three consecutive sputum smears have yielded negative results for tuberculosis. Those with new positive skin tests who are without clinical disease should be evaluated and counseled for preventive therapy against tuberculosis. Prophylaxis is not imperative, and those who choose not to take therapy may not necessarily be excluded from work unless active disease is diagnosed. However, the risk of transmission to the HIV population is great and must be accounted for in determining work status and assignments.[228]

For HIV-positive health-care workers, prophylactic therapy is indicated whenever contact is made with an individual with infectious tuberculosis.[30] Preventive therapy is appropriate despite a negative PPD, and repeated courses are appropriate with each subsequent exposure. For those who show PPD reactivity, treatment with isoniazid for 12 months is indicated.[234] In all HIV-infected individuals, a reaction of $\geq$ 5 mm is considered positive as opposed to the 10-mm induration considered positive in others.[228] This is due to the relative hyporeactivity to skin antigens demonstrated by those with HIV.

Pentamidine & Ribavirin Exposure

In addition to the potential for infection, there are toxic aerosols that must be dealt with appropriately. Pentamidine and ribavirin have received a great deal of attention. Ribavirin has been shown to produce teratogenic effects in hamsters, rats, and rabbits.[235-238] These effects are dramatic and include malformations of the skull and skeleton, gastrointestinal disturbances, and decreased survival of offspring. A study using baboons did not show similar effects.[238] The studies involving the rodent models have been criticized because ribavirin was given orally, and the blood levels achieved were much greater than those achieved through aerosolization.[239]

In studies of occupational exposure to ribavirin in respiratory care practitioners and nurses,[240-242] only one nurse has demonstrated a detectable ribavirin concentration in the blood.[241] Kacmarek cautions against a flippant treatment of this data, however.[243] First, investigators failed to monitor the caregivers over a period that accurately represents the respiratory syncytial virus "season" when chronic exposure occurs. Second, the detection limit in blood used in these studies may not be appropriate in that it does not account for the high solubility of ribavirin in water. Complaints associated with ribavirin exposure include irritation of the eyes, nose, throat, and airways.

Studies evaluating the teratogenicity of pentamidine are not available. A decreased diffusing capacity has been documented in 1 respiratory care practitioner chronically exposed to pentamidine for 18 months.[244] Other complaints noted by practitioners administering pentamidine treatments without barrier masks include shortness of breath, cough, chest tightness, burning of eyes, nose and throat, sinus irritation, sneezing, nausea, lightheadedness, and headache.

Because it is unclear to what degree exposure to either ribavirin or pentamidine is important, we believe that respiratory care practitioners must be responsible during aerosol administration. Particulate respirators must be worn during aerosol delivery, and gloves should be worn when medications are prepared and nebulization equipment is cleaned. Treatments should be given only in rooms with negative airflow of at least 6 air exchanges/hour, and with high-efficiency particulate air (HEPA) filters, or in booths or hoods with aerosol exhaust capabilities. The optimal nebulizer design includes exhalation filters and hand control of aerosolization. Ribavirin aerosol delivery should be interrupted for at least 5 minutes before tents, hoods, and ventilation circuits are entered. When ribavirin is being delivered via tent or hood, vacuum containment systems should be applied[245,246] or the Aerosol Delivery Hood System (ICN Pharmaceuticals Inc, Costa Mesa, CA) should be utilized. Pregnant health-care workers should be discouraged from any exposure to either ribavirin or pentamidine.

Cross-Contamination

The last major area of concern regarding patient safety is cross-contamination from dirty equipment. The importance of strict adherence to proper procedures for cleaning and disinfection of all respiratory therapy equipment, pulmonary function laboratory equipment, and bronchoscopic equipment must be reemphasized. The potential is high for respiratory therapy equipment to harbor agents of nosocomial pneumonia, such as *Pseudomonas aeruginosa* and other Gram-negative bacilli.

The opportunistic pathogens associated with HIV disease pose a much greater threat to the immunocompromised host. Failure to properly disinfect flexible bronchoscopes resulted in tuberculosis infection in subsequent patients who underwent bronchoscopy.[247,248] The ability of HIV to survive for prolonged periods under various environmental conditions is also a cause for concern.[249] Several studies have demonstrated that a variety of disinfecting agents are capable of inactivating HIV.[249-251] Most of these agents are commonly used by respiratory care practitioners. It is important that specific CDC recommendations for prevention of HIV cross-contamination be followed.[217] All equipment that touches mucous membranes should be sterilized or receive high-level disinfection, ie, the equipment should be subjected to an agent such as glutaraldehyde, hydrogen peroxide, ethyl alcohol, or chlorine, capable

of killing all microorganisms except bacterial endospores.[216] Before disinfection can take place, however, it is essential that organic material (such as serum, sputum, blood, and pus) be removed from equipment. These substances may act as barriers to the chemical properties of the disinfectant. As an alternative, equipment may be gas sterilized with ethylene oxide, but this may remove equipment from service for much longer periods of time. It is imperative that specific instructions regarding exposure time, concentration, temperature, and pH be followed to ensure optimal disinfection. In our institution, bronchoscopes are disinfected with a Hibiclens solution (Stuart Pharmaceuticals, Wilmington DE) prior to ethylene oxide sterilization. Pulmonary function testing equipment is best maintained by first cleaning disassembled devices with a detergent in water, then disinfecting with a high-level disinfectant, and autoclaving or gas sterilizing.[216] Disposable mouthpieces and tubing should be used whenever possible.

Bioethics

In her pursuit to better understand issues involved in the care of AIDS patients, one resident physician stated that "for all the dizzying medical difficulties of the disease, its ethical difficulties were even greater."[252] Most health-care professionals would probably agree. Respiratory care practitioners deal with a number of ethically challenging issues in the care of AIDS patients including transmission risks and mandatory HIV testing, decisions regarding life support measures, and concerns over the limits of one's ability to comfort the sick and the dying. On a larger scale, the scarcity and allocation of health-care resources, the uncertainties of experimental therapies, and confrontations with one's own mortality, prejudice, and fears challenge health-care providers daily. These issues are substantial stressors that, in some instances, may limit the practitioner's effectiveness in caring for AIDS patients.

Fear of transmission of the virus is a potent stressor. Anger stemming from the feeling of being placed in a treacherous situation, in which one does not have control, may inhibit good care of the patient. O'Donnell and colleagues[253] found that the job categories of health-care workers who felt themselves to be at greatest risk for contracting AIDS also represented those who felt that they could be infected through casual contact. Respiratory care practitioners possess the knowledge and understanding to allay these fears. We believe that clearing the confusion about the transmissibility of AIDS will improve communication and reduce discriminatory behaviors on the part of health-care workers towards infected patients. In this same study, the employees surveyed described a reduction in stress with increasing patient contact, especially when such contact involved interactions of a social nature.[253]

Another stressor is the helplessness that health-care professionals feel in their care of AIDS patients. Respiratory care practitioners may be especially prone to such feelings when they play a role in the mechanical ventilatory support of patients. Pathogens resistant to chemotherapeutic agents and pulmonary physiology unresponsive to the 'cutting-edge' technology of ventilators can discourage exploration into therapeutic options. Yet, aggressive medical intervention does not always constitute good care. A difficult ethical dilemma exists between sustaining a patient in the hope of successful treatment and maintaining comfort and dignity.

In 1990, two groups described guidelines to use in determining who would be mechanically supported for respiratory failure secondary to *P. carinii*.[127,254] Based on the available data characterizing survivors and nonsurvivors, these groups recommended mechanical ventilation for patients with a first infection of *P. carinii* who were in good general condition and who wished to be intubated. More recently, further study by Dohn et al[255] has shown that there is no statistically significant difference in survival between the first episode of *P. carinii* pneumonia and the second episode of *P. carinii* progressing to respiratory failure. Montaner et al[256] determined that serum LDH levels and a scoring system of organ failure predicted mortality in patients with *P. carinii* pneumonia progressing to respiratory failure. The study concluded that patients with LDH levels > 750 U/L and failure of at least one other organ system besides the lungs had greater mortality than those patients with LDH levels < 750 U/L and only pulmonary involvement. All patients in that series with involvement of 4 or more organs and LDH levels > 2,500 U/L died.

As we are all aware, multiple organ system failure is frequently associated with a significant mortality, and the secondary feeling of futility is noted by health-care workers. Futility itself is a great stressor for health-care workers. When therapies are perceived to be futile, health-care professionals may feel helpless, discouraged, and inadequate. A lack of understanding regarding the boundaries of what constitutes futility may also be frustrating. Schneiderman et al[257] have suggested that a therapy that has failed 100 times is futile. Furthermore, if a treatment merely preserves unconsciousness or fails to free one from life-support measures, thereby preserving biologic life without autonomy, it should be considered futile. The Bioethics Task Force of the American Thoracic Society endorsed this view, unless a prior statement by the patient expressed a contrary desire.[258] The withdrawal of life support measures may be perceived by the health-care provider as a violation of the commitment to care for the patient.[259] Some may find it easier not to begin a therapy, such as mechanical ventilation, than to withdraw it later. The obvious consequences of withdrawing treatment render it a less attractive option. Application of mechanical ventilation may be seen as simply prolonging the inevitable. However, ethicists generally agree that it is ethically and morally preferable to try a treatment and then withdraw it if it proves futile than not to try it at all.[259]

The use of the Durable Power of Attorney for Health Care (DPAHC) may help clarify the ethical issues surrounding

life support in critically ill patients. This type of advance directive leaves value judgments and decision making to the patient and his or her proxy, thus placing less pressure on the health-care team to decide on the best therapeutic plan. The DPAHC grants legal recognition of another (a proxy or agent) appointed by the patient to make decisions on his or her behalf when the patient is unable to do so. The agent or proxy is a person who should be familiar with the expressed desires of the patient regarding aggressive care. Since the implementation of the Patient Self-Determination Act in 1991, hospitals have been required to provide education and choice to patients regarding the execution of advance directives.

One final issue that may be contrary to the element of choice among treatment options is the issue of the allocation of health-care services. Indeed, the AIDS epidemic has placed a burden on the health-care system. One example is multidrug resistance, which requires additional resources for the development of alternative chemotherapeutic agents, a greater surveillance of patients for treatment compliance, and prolonged hospital stays and surgeries.[29] Some patients with AIDS present to health-care facilities in the advanced stages of disease,[4] which may greatly increase costs to the system by having to provide more expensive intervention at a time when patients are unable to pay, and poses a greater likelihood that communicable diseases may be spread more widely. Will the existing health-care system manage these additional pressures? How much money can be allocated for AIDS education, treatment, and basic research?

It is clear that the future holds greater challenges to our national resources. The epidemic is spreading. Between 1984 and 1990, the case burden for five major U.S. cities decreased from 63% to 38%,[260] and the percentage of new cases in the homosexual population has been decreasing, but there has been a dramatic increase in the number of intravenous drug abusers, women, and teen-aged youth with the disease.[259] Current projections show that African-Americans, Hispanics, homosexual men, and adolescents will continue to constitute the majority of those affected.[260] Projections of the number of cases in the United States by the 21st century vary, ranging from 1.5 million to 14.5 million. Though the number may not be accurately predicted, experts agree that the opening of the new century will be "the time of AIDS."[262]

By 1990, 24 million dollars had been spent to support 11 different vaccine trials.[263] More funds were spent on the testing of 70 drug protocols. The merits of basic research in the HIV arena should not be questioned; however, despite the monies spent, curative treatments and/or vaccines remain elusive.[264] Successes with treatments aimed at early intervention are providing optimism for patients and health-care providers alike. Dr Mathilde Krim, one of the founders of the American Federation for AIDS Research (AMFAR) has stated, "Within my lifetime, people with AIDS may live long, normal lives, receiving regular treatments."[262]

In Conclusion

As the public policy debate over health-care reform continues, respiratory care practitioners may find themselves practicing in tuberculosis sanitariums not unlike those of yesteryear. In an effort to minimize costs without compromising quality of care, specialized AIDS-care institutions may become the norm. In a similar way, greater involvement for practitioners may be realized in outpatient clinics, hospice care, AIDS day-care centers, and in home-health care. Regardless of the facility, the respiratory care practitioner should assure the maintenance of a good therapeutic environment for AIDS care. As patient advocates, informed caregivers may also contribute greater understanding to the ongoing challenges of medical science, ethics, and public policy. Participation in determining the effectiveness of medical intervention for AIDS patients provides a significant ongoing role for practitioners. Whether aerosolized pentamidine will continue to be standard therapy for *P. carinii* prophylaxis, and whether diagnosis of pulmonary infections can be improved using newer, less costly techniques are just two of the avenues of exploration to which practitioners may contribute. As we move toward a new millennium, respiratory care practitioners can and must be expected to participate in the challenge of the AIDS epidemic.

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Psychological Issues in the Ventilator-Dependent Patient

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Introduction

It is commonly accepted that psychological problems frequently have an adverse effect on weaning patients from mechanical ventilation; however, data examining psychological function in patients receiving ventilatory support are extremely limited.[1] This is somewhat surprising because many factors reported to have an adverse effect on psychological function (eg, ICU environment, dependence on machines for life support, and the presence of underlying chronic illness) are commonly present in the ventilator-dependent patient. In addition, underlying cardiopulmonary disorders that cause chronic hypoxemia or hypercapnia or that require medications that impair psychological function are routinely found in the ventilator-dependent patient. Finally, the implementation of mechanical ventilation itself impedes natural communication, renders the patient immobile, promotes the loss of independent function, and, thereby, contributes to a patient's increased sense of apprehension and/or feelings of isolation. All of these

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factors, either singly or in aggregate may enhance the development of psychological disorders.

In this review, we attempt to integrate information about psychological problems in patients with pulmonary disorders, critical illnesses, and chronic diseases with the limited data that exist in patients receiving prolonged ventilation. Moreover, we attempt to use this information to develop an effective strategy to aid the respiratory therapist and other members of the treatment team in the evaluation and therapy of psychological issues in the ventilator-dependent patient.

Psychological Problems Encountered in ICU Patients

Because most, if not all, patients who receive mechanical ventilation have at least a portion, if not all of their care provided in the ICU, psychological problems arising in ICU patients may provide insight into the psychological disturbances that arise in those receiving mechanical ventilation. It is reported that non-ICU patients experience psychological disturbances less than 1% of the time. In comparison, 14-72% of ICU patients experience psychological problems—ranging from anxiety, apathy, and agitation to fear, depression, and delirium. Delirium is an acute organic brain syndrome characterized by progressive disorientation to person, place, and time, and is associated with varying levels of cognitive embarrassment. Delirium is a serious problem when it arises and is a result of cerebral insufficiency secondary to metabolic, toxic, anoxic, or infectious injuries to the brain that if left untreated account for a mortality of 30%. Overall, the etiology of psychological disturbances in critically ill ICU patients is thought to be multifactorial and includes psychological derangements resulting from the severity of the underlying illness, the person's age, the adverse effect of medications, poor baseline psychological function, or the effect of the ICU environment on sleep and sensory deprivation.

Incidence

Kornfeld and colleagues [2] were among the first to describe the incidence and types of psychological disturbances that arise in ICU patients. In postoperative adult open-heart-surgery patients, they found that 38% of patients developed delirium, characterized by progressive disorientation to person, place, and time, that was associated with various degrees of cognitive impairment. The authors noted that delirium was more likely to develop in the patients who were most ill or in those who required a longer time on circulatory bypass. In most cases, delirium arose within the first 3 to 5 postoperative days and eventually resolved 1 to 2 days following transfer to a routine hospital bed. Egerton and Kay,[3] Blachy and Starr,[4] and Rubinstein and Thomas[5] confirmed these findings and further reported that delirium or other psychological disturbances complicated the postoperative period of open heart surgery in 25-57% of their patients. Hackett et al[6] found that 47% of their patients admitted to a CCU for 5 days or longer became temporally disorientated to time of day, day of week, or time of year. Although the exact causes for the development of cognitive disturbances were not provided in any of these studies, several factors that they believe important to the development of psychological problems were highlighted by the authors. The most important of these etiologies included the severity of underlying illness, sleep deprivation, and sensory deprivation.

Etiologies of Psychological Disturbances

The Severity of Illness

Blachy and Starr[4] found severity of illness to be closely associated with the onset of psychological disturbances. They found that patients with American Heart Association Class I congestive heart failure (CHF) had a 29% incidence of delirium after cardiotomy; however, the incidence increased to 100% in patient's with perioperative Class-IV CHF. Moreover, they found that the duration of cardiopulmonary bypass and the complexity of the underlying operative procedure further increased the risk for development of postoperative delirium. Although they were unclear as to the exact causes of the higher incidence of psychological disturbances in the more ill patients, they speculated that subclinical infection, anoxia, and a higher incidence of electrolyte disturbances may have been present.

Sleep Deprivation

The ICU is designed to provide optimum critical care with a multitude of monitoring equipment that includes many visual and auditory alarms and frequent patient assessment, performed in a clean but stark and sterile environment. The unfortunate result is that this type of environment can be an important contributor to sleep deprivation, a condition reported to enhance the development of psychological problems.[4] In most studies, restless sleep, nightmares, and the total absence of dreaming during sleep are commonly reported in ICU patients who develop delirium or other psychological problems. Sleep disorders also appear to be a common finding in a significant number of ICU patients despite the absence of psychological problems. In patients from the general population who present for evaluation of psychological disorders, it is estimated that approximately one third suffer from an underlying sleep disorder.[7] Berlin and colleagues[8] have reported that over 80% of patients who require hospitalization for acute medical problems and psychological consultation are found to have underlying sleep disorders.

Although, data regarding sleep and psychological function in critically ill patients are limited, several investigators have shown that disturbed sleep patterns frequently precede the onset of psychological disorders. Sveinsson[9] found sleep deprivation commonly present before the onset of delirium and perceptual problems in his patients following cardiac surgery.

Egerton and Kay[3] found that one to two sleepless nights preceded the onset of delirium that developed in 40-60% of their postoperative open-heart-surgery patients. Hackett and colleagues[6] observed that 75% of patients admitted to an ICU for an average of 5 days or greater denied any dreaming and that 7 of 10 patients who did dream, reported terrifying nightmares. Kornfeld[2] and Hackett and colleagues[6] found nightmares most vivid and intense in patients who had survived cardiac arrest; and these dreams were frequently associated with the development of insomnia. Most critically ill patients who recover recall the content of their dreams as persecutional in nature and find that the substance of their dreams usually arises as distortions of treatment regimes encountered in the ICU.[10,11]

Several factors inherent in the care of the critically ill contribute to the development of disturbed sleep. Egerton and Kay[3] found that the level of noise generated in the ICU by patient-staff conversation and staff activity contributed greatly to interrupted sleep. In addition to staff activity, ICU equipment (eg, monitors, ventilators) significantly contribute to elevated ICU noise levels. In one study that measured mean noise levels at the head of ICU beds,[12] it was found that the noise levels generated by monitors, ventilators, and oxygen outlets, were equivalent to a radio playing at full volume, 90% of the time.

In addition to ongoing noise, nighttime nursing and medical interventions required to treat the patient's underlying illnesses are not conducive to restful sleep. Sleep is a cyclical process. The normal adult alternates between nonrapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep. Sleep phases cycle approximately 5 times over an 8-hour period, with approximately 25% of that time spent in REM sleep. Critically ill ICU patients who require multiple interventions may not experience even one full uninterrupted sleep cycle, depending on the nature of their underlying illness, and this pattern may continue for several consecutive nights. Aurell and Elmquist[13] performed sleep studies in 9 ICU patients for 2-4 consecutive nights and documented that all patients had fewer than 2 hours of total sleep time, no patient demonstrated REM sleep, and all patients showed severe reductions in the duration of Sleep Stages 3 and 4.

Medications frequently used in treating critically ill ICU patients may also adversely affect sleep quality. Barbiturates, narcotic analgesics, catecholamines, and long-acting benzodiazepines have all been reported to either significantly reduce or delay the onset of REM sleep.[14]

Another important factor that may affect sleep quality in the ICU patient is the common failure of physicians and nurses to recognize the importance of sleep quality and to make appropriate interventions to ensure the adequacy of sleep. In the study by Aurell and Elmquist,[13] nurses in the ICU reported that patients had slept all night despite concurrent polysomnographic studies demonstrating that no patients had slept more than 2 hours. Similar findings were reported in hospitalized non-ICU patients studied by Berlin and colleagues[8] who found that 54% of the patients who had significant sleep disorders had no documentation of sleep quality in physician or nursing notes. Greater awareness of the necessity for restful sleep and the knowledge of the appropriate measures needed to ensure adequate sleep are required by all practitioners caring for critically ill patients.

Sensory Deprivation

Besides contributing to sleep deprivation, the ICU enforces sensory deprivation that may contribute to the development of psychological problems. Wilson[15] compared the incidence of delirium in 50 postoperative patients treated for 3 or more days in an ICU location without windows to 50 postoperative patients treated in an ICU with windows providing a view. Although, patients in both units did not differ in age, operative procedure, or nursing care, patients treated in the windowless ICU had a threefold greater incidence of postoperative delirium. It is conceivable that the absence of windows fostered a sense of isolation and limited the ability of postoperative critically ill patients to orient themselves to time of day and season of the year.

Besides sensory deprivation, monotonous sensory input has also been reported to induce disordered thought processes and even hallucinations.[16] For the most part, an ICU patient's visual stimulus is restricted to the monochromatic overhead ceiling tiles or surrounding unadorned plain white walls. Acoustic stimulation is also limited in the ICU and consists almost entirely of the monotonous sounds of beeping monitors and feeding pumps and the harsh noises emitted from ventilators and oxygen and gas outlets. Neher[17] reported in normal subjects that intermittent monotonous auditory stimulation may induce auditory and visual hallucinations in normal subjects. Egerton and Kay[3] speculated that exposing open-heart-surgery patients to auditory driving by one to six clicks of sound per second may have provoked disordered thought processes and hallucinations. Thus, it appears that a variety of abnormal auditory and visual stimulation routinely encountered during the process of long-term ventilation in the ICU may predispose susceptible patients to the development of psychological disturbances.

Contributing Special Factors

In addition to factors in the ICU that may predispose ventilator-dependent patients to psychological problems, the underlying pulmonary disease, its medical treatment, and the process of mechanical ventilation itself may all independently contribute to the development of psychological problems.

Effect of Lung Disease on Psychological Function

Personality & the Pulmonary Patient

In an attempt to better understand the psychological function of patients with underlying pulmonary diseases, sever-

al studies have characterized the psychological features and personality of patients with disorders, such as chronic obstructive pulmonary disease. Traits, such as anxiety, chronic fatigue, depression, coping difficulties, and somatic preoccupation, are commonly reported in these patients.[18,19] Although studies conducted in patients with different chronic illnesses suggest that the severity of the patient's illness, rather than the nature of the disease, correlates best with the degree of psychological distress,[20] several investigators have noted a distinctive self-perpetuating pattern in the psychological complaints of COPD patients.[21] Based on these studies, therefore, patients with underlying illnesses such as COPD who require mechanical ventilation may have a predisposition to psychological adjustment disorders.

Gas Exchange Abnormalities

Abnormalities in gas exchange commonly present in ventilator-dependent patients may have a significant effect on psychological function. The hypoxemia and hypercapnia found in many ventilator-dependent patients are associated with a variety of psychological complaints and cognitive impairment, including inappropriate behaviors, impaired short-term memory, perceptual disorders, and indifference or inattention. In a multicentered study that examined the efficacy of nocturnal versus continuous oxygen in hypoxemic COPD patients, Grant and colleagues[22] found that cognitive impairment was three times more common in hypoxemic COPD patients compared to nonhypoxemic subjects matched for age, sex, and psychological status. They found that higher cognitive functions (eg, complex perceptual motor integration and abstraction) were most severely affected in hypoxemic COPD patients, and 50% of the patients showed significant decrements in strength, coordination, and motor skills. In a follow-up study, Heaton et al[23] found that hypoxemic COPD patients performed better on neuropsychological testing after 12 months of continuous oxygen therapy compared to patients treated with only nocturnal oxygen administration. These two studies imply that cognitive embarrassment is commonly found in patients with COPD and may be exacerbated by the presence of hypoxemia. It further suggests that the use of supplemental oxygen may have a significant effect on improving psychological function.

Cognitive Deficits

In an attempt to identify the prevalence of cognitive disturbances in patients who require long-term ventilator support, we recently evaluated the prevalence and distribution of neuropsychological deficits in ventilator-dependent patients admitted to a tertiary care ventilator rehabilitation unit.[24] A skilled clinical psychologist performed bedside neurologic assessments in 28 patients requiring mechanical ventilation for a minimum of 21 days. Figure 1 shows the type of deficits that were present in the 28 patients receiving prolonged ventilation. Memory was most frequently impaired; 86% of patients had deficits in short-term recall ability. Impaired reasoning and disorientation were observed in 50% of the patients, and 36% of the patients had impaired long-term memory and language function. Figure 2 shows the distribution of cognitive deficits across all patients. Most patients had deficits in 3 or more cognitive functions, and only 7% of patients had no cognitive deficit. These data, although preliminary, suggest that cognitive deficits are common in patients receiving

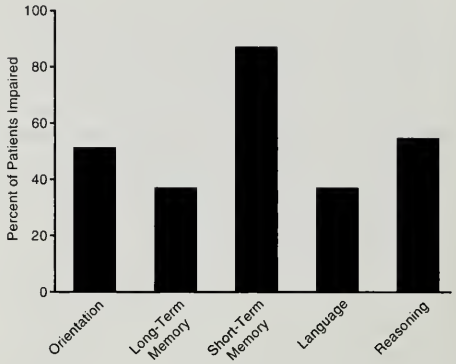

Fig. 1. The presence of cognitive deficits in 28 patients receiving long-term ventilation. Short-term memory was most frequently impaired. In 50% of patients, impaired reasoning and disorientation were observed; impaired long-term memory and language function were abnormal in 36% of the patients studied. (Reprinted from Reference 24, with permission.)

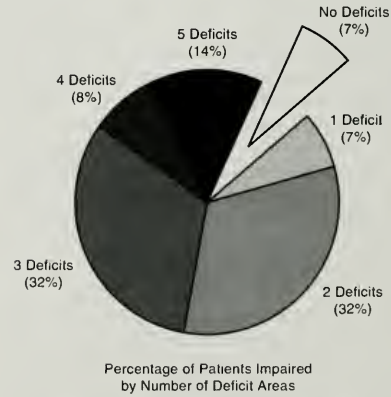

Fig. 2. Specific cognitive deficits in all ventilated patients. Of patients tested, 93% showed abnormalities in cognition. Most patients showed several cognitive deficits. (Reprinted from Reference 24, with permission.)

prolonged ventilation and may be important factors in the development of psychological problems.

Chronic Dyspnea

In some patients, the cause for dyspnea may be unclear but may be significant in limiting their ability to tolerate ventilator support or wean efficiently. The lack of clear-cut causes for failed weaning may be misinterpreted by caregivers as a lack of patient cooperation or submaximal effort. The sensation of dyspnea may also be important in the patient's psychological perception of breathing or weaning from ventilator support. Dyspnea is a subjective complaint that may produce a feeling of anxiety that, in turn, increases the sensation of dyspnea independent of any physiologic changes. In many patients, the feeling of dyspnea leads to a decreased expression of any emotion because even positive emotions, such as joy, can lead to changes in oxygen demand and increase the sensation of dyspnea. In response to this vicious cycle, patients may decrease the expression of any emotion and the patient is typically described as living in an "emotional straight jacket."[21] Preceding the implementation of mechanical ventilation, some pulmonary patients may have developed a decreased tolerance for breathlessness over time and display anxiety or avoidance in anticipation of any physical activity that they feel will increase their sensation of dyspnea. In some patients receiving long-term ventilation, the initiation of weaning trials or physical exercise programs can provoke anxiety and fear that is more related to the perception of dyspnea than to the stress of the activity itself.

Pulmonary Medications

Medications routinely used to treat pulmonary illnesses can produce a host of psychological and behavioral side effects. For example, agitation and excitation may result from the use of sympathomimetic agents, and affective disturbances and inappropriate behaviors can occur with steroid treatment.

Aminophylline has been reported to affect patient mood, behavior, and performance on neuropsychological testing. Young et al[25] demonstrated that the administration of theophylline produced a substantial drop in regional cerebral blood flow (rCBF) in five patients with severe COPD—an average decrease of 26% following a loading dose and of 22% with maintenance doses. The investigators speculated that a decrease in rCBF contributed to neuropsychological disturbances in COPD patients; however, they failed to report the patient's baseline psychological function, and no correlation was made between neuropsychological function and rCBF. On the other hand, Lindgren et al[26] reported that chronic theophylline administration had no significant effect on academic achievement in 85 school-aged asthmatic children compared with a normal sibling control group. At the present time, data regarding theophylline use and psychological function is contradictory and awaits further study.

The administration of steroids has been implicated in the development of neuropsychological disturbances in a number of case reports. Schraa and Dirks[27] studied the effects of ACTH on cerebral function and found that exogenous corticosteroid therapy has a significant negative effect on attention span and memory function. A comprehensive review of more than 700 consecutively hospitalized patients treated with corticosteroids found a dose-dependent effect of corticosteroid administration on psychological disturbances.[28] In those patients who received < 40 mg of prednisone/day, the incidence of psychiatric problems was only 1%, compared with an incidence of psychological dysfunction of ≥ 5% in patients receiving 40-80 mg of prednisone and 18% in patients receiving > 80 mg of prednisone/day. Although, the effect of chronic corticosteroid therapy on cognitive function in patients with pulmonary disease is limited, Smyllie and Connolly[29] found a ≤ 2% incidence of psychological problems in 520 patients who received ≥ 20 mg of prednisone/day. These data suggest that corticosteroid therapy may have an important effect on memory and attention span in some patients, but, in most cases, noteworthy psychological problems were minimal when prednisone doses were ≤ 20 mg/day.

Impact of Prolonged Mechanical Ventilation

In addition to the stress facing every critically ill patient, ventilator-dependent patients experience the unique stress of depending on a machine for breathing moment to moment, hour to hour, and day to day. Some recent studies have reviewed the feelings reported by patients who have experienced prolonged ventilatory support. Riggio and colleagues[30] described the perceptions of ventilated patients about the sources for their psychological stress and found that the inability to communicate, disorientation, memory loss, and pain and discomfort were all perceived as major problems.

The patient's recall of reactions to mechanical ventilation after hospital discharge was further assessed by Bergbom-Engberg and Haljamae.[31] They found that 47% of patients reported feeling anxious or fearful during mechanical ventilation, and 90% recalled the experience as stressful or unpleasant as long as 4 years after the episode.

A number of emotional stressors specific to ventilator treatment have been recognized. The process of mechanical ventilation necessitates the loss of independence and control over the most vital, voluntary life-sustaining activity—breathing. Endotracheal and tracheostomy tubes impair the ability of patients to speak, but patients also cannot sigh, gasp, sneeze or produce other emotional expressions that are part of the usual body-language vocabulary. Gale and O'Shanick[32] have characterized a patient's inability to communicate while being ventilated as communicator isolation. The inability of ventilated patients to fully communicate their physical and emotional needs to others can create further feelings of isolation and abandonment.

Other aspects of ventilator care have also been described as additional sources of stress. Most ventilated patients describe endotracheal suctioning as extremely unpleasant and compare suctioning with gagging or suffocating. The monotonous noises emitted by mechanical ventilators are unnatural and further contribute to aberrant sensory input and disturbed sleep. Limitations in ambulation induced by ventilator support may further contribute to feelings of patient isolation. Finally, patients on ventilator support are faced with the possibility that equipment failure at any moment might result in their death. The incessant sounding of ventilator alarms may, therefore, be perceived as a serious development (eg, mechanical failure) and contribute greatly to their feelings of apprehension and anxiety and even, in some, a sense of impending death.

In summary, the stresses faced by the ventilator-dependent patient are similar to those encountered by other critically ill patients but includes the added stress of continuous dependence on a machine for breathing. The complex interactions between physiologic changes caused by the underlying pulmonary disorder and dependence on life-sustaining technology that limits the ability to communicate results in a combination of factors that may precipitate or amplify the development of psychological disturbances specific to the ventilated patient.

Evaluation of Psychological Disturbances

The assessment of psychological function and the impact of psychological stress in the patient receiving prolonged ventilation falls well within the evaluation skills of the clinical management team. Psychological assessment can be incorporated into the routine assessments conducted by physicians, nurses, and respiratory and rehabilitation therapists. A psychologist or psychiatrist can provide important additional information to the management team, but participation by a mental-health professional is not a prerequisite for measuring and addressing psychological issues.

The evaluation of psychological function begins with a comprehensive history and physical exam. In contrast to the routine examination, however, the quality of the psychological assessment is largely influenced by the communication skills of the interviewer. An initial successful patient encounter will have a positive impact on establishing a good rapport with the patient and facilitate the completion of a thorough psychological examination. Throughout the initial assessment, the interviewer should be supportive and reassuring and use nonverbal skills, such as, direct eye contact with the patient. The main goal of the psychological examination is to identify factors that may contribute to or exacerbate the patient's present psychological state. Three broad areas should be assessed during the psychological exam: features of the underlying disease; aspects of the underlying psychological status, and reactions specific to the medical treatment.

The course of a patient's disease plays a large role in determining how the patient reacts to the stresses of the illness in general and to specific treatments and medical interventions. For example, there may be a marked difference in the reaction of the patient receiving mechanical ventilation for the first time compared to the reaction of the patient who has received mechanical ventilation several previous times for a chronic illness, such as COPD. The patient experiencing the initial bout of respiratory failure is usually fearful and bewildered by ventilator support but has a hopeful outlook and high expectations for weaning and functional improvement. By contrast, the previously ventilated patient is more familiar with ventilator support but is less hopeful and more discouraged about the eventual outcome.

An additional consideration is the premorbid level of function of the patient, prior to being placed on ventilatory support. Many patients with chronic respiratory disorders, severely restrict their daily activities and level of independence as dyspnea and fatigability increase. This may result in patients' lowering their expectations about optimal functioning once discharged. It is important for the clinical management team to establish realistic goals for the patient and family about the highest level of activity that can be achieved relative to the underlying disease process.

A good psychological history should include questions about the patient's past learning behavior, marital discord, family support, socioeconomic status, prior education background, living arrangement, work history, and alcohol and drug use. The interviewer should also query patients about psychiatric symptoms in themselves or their family and their style of coping with and adjustment to physical illness or death.

The interview should also determine whether the patient is experiencing frank psychiatric symptoms, such as visual or auditory hallucinations, delusions, or paranoid ideations. Mental status and cognitive function can be objectively assessed using standardized bedside neuropsychological tests (eg, the Mini-Mental Status Examination[33]). Facets of function to be evaluated include orientation to person, place, and time, capacity for sustained attention, immediate and delayed memory function, and reasoning ability. Other skills that can be assessed in the interview process include motor function, long-term memory, receptive and expressive language function, visual skills, reading ability, and the patient's thought process. Psychological issues should also be evaluated in relationship to the process of mechanical ventilation. It is important to assess symptoms of delirium associated with sleep and sensory deprivation and to establish the patient's level of orientation to person, place, and time, but it is also important to assess symptoms in response to aspects of the daily management plan including scheduled treatments, rehabilitation therapies, and interactions with members of the management team.

Psychological problems related to the process of weaning are especially important. An assessment of the patient's perception of the ventilator apparatus, the process of weaning from ventilation, and goals for weaning should be re-

viewed. Weaning may be perceived differently by individual patients, and it is important to ascertain the patient's perspective prior to implementing weaning trials. For example, weaning may be viewed as a significant improvement in some patients because their ability to verbally communicate will become enhanced and they will become more mobile. By contrast, other patients may view weaning as uncomfortable and anxiety provoking without any clear-cut gains to be obtained. Patients may also misunderstand the weaning process, lack confidence in the ability to breath without the ventilator, feel unable to regulate breathing, or, in some respects, feel abandoned by the treatment staff. The patient's perception of the weaning process, goals for weaning outcome, and the likelihood of weaning success should be established beforehand to minimize the development of psychological dysfunction during the weaning process.

Treatment of Psychological Problems

General Approach

The general approach to the treatment of psychological problems in the ventilator-dependent patient combines the basic principles used to treat psychological disorders in patients suffering from advanced lung disease or critical illnesses coupled with the treatment plan directed at the special problems posed by the process of mechanical ventilation. Factors contributing to the development of psychological problems precipitated by the process of mechanical ventilation (eg, limited mobility, impaired communication, ICU environment) should be identified and systematically resolved in order to improve the patient's sense of control over the situation and ability to communicate appropriately with the treatment staff. It is paramount to provide an environmental setting that minimizes patient seclusion and maximizes interaction with the staff and the patient's family. As previously discussed, several studies have documented the intellectual impairment observed in ICU patients, which is characterized by perceptual distortions, confusion, and disorientation that may arise in large part from the environmental constraints of the ICU.

To decrease the incidence of environmentally mediated psychological problems, Kornfeld[34] has proposed several modifications in patient care: (1) maximizing periods of uninterrupted sleep by minimizing nighttime interventions; (2) placing each patient in an individual room; (3) placing nonessential monitoring equipment outside of the patient's rooms to reduce the amount of monotonous auditory input; (4) placing orientation aids, such as calendars, clocks, and artifacts in the patient's room; (5) making an outside window visible to each ventilated patient and; (6) increasing patient mobility.

An additional goal of psychological treatment is minimization of conditions that contribute to disorientation and confusion by providing compensatory strategies for major cognitive problems. As previously described, ventilator-dependent patients are prone to cognitive disorders including impaired memory and orientation, as well as deficits in abstract reasoning and verbal functioning.[24] Compensatory strategies for these problems include repeating information in a simplified manner, delivering information both verbally and visually, using illustrative aids and gestures, and continuing to monitor the patient's recall and understanding of instructions and information provided. By systematically providing cues and compensatory strategies for these cognitive impairments, deficits that could interfere with teaching and rehabilitation activities can be substantially minimized.

Communication & Swallowing

An important step to involve patients in their care and minimize cognitive disturbances is the re-establishment of the ability to communicate. Previous studies have shown that impaired communication is one of the most common features that contribute to poor tolerance of mechanical ventilation. In addition, improved communication among ventilator-dependent patients, their families, and the staff decreases stress, improves decision-making, and decreases the likelihood of developing feelings of isolation and/or abandonment. Several modalities are now available to facilitate written or verbal communication in patients receiving mechanical ventilation. Some of these methods can be employed while patients are on full ventilatory support (eg, buccal resonator, 'talk trach', electrolarynx) or during periods of spontaneous breathing by using devices that redirect airflow through the vocal cords and permit more natural speech (fenestrated tracheostomy tube, Passy-Muir valve). Irrespective of the method chosen, the entire staff should encourage the patient to use the device consistently to facilitate verbal expression and decrease feelings of isolation.

Besides communication, one of the most important natural processes to restore in recovering, critically ill ventilator-dependent patients is eating. Besides the obvious important role in providing nutrition, eating rather than being fed by artificial means fosters a sense of independence, social interaction, patient control, and enjoyment that can provide a significant emotional uplift for patients who have been receiving prolonged ventilatory support. Although swallowing dysfunction is commonly encountered in patients receiving prolonged ventilator support,[35] swallowing reconditioning and treatment measures implemented after evaluation by an experienced speech pathologist can help to restore successful oral intake in most patients. In our experience, the majority of our long-term ventilator-dependent patients have improved swallowing and are able to eat after the implementation of compensatory strategies (eg, altering the consistency of food, making repetitive swallows after a bolus of food, and adjusting the position of the head during eating). In most cases, the reinstitution of feeding provides an emotional uplift for patients that becomes an important milepost in their recovery.

Medications

In addition to behavioral techniques and supportive psychotherapy, some patients receiving long-term ventilation may benefit from the selective use of psychotropic medications.[21] Anxiolytics, such as, benzodiazepines may be useful in some patients who suffer from extreme anxiety. In other ventilated patients, small doses of neuroleptic agents may be helpful in controlling agitation. In others, antidepressant agents may be needed to treat extreme fatigue and apathy.

Comprehensive Multidisciplinary Programs

Studies conducted in patients with COPD[36] and those receiving chronic mechanical ventilation[37] have demonstrated that involvement in a comprehensive rehabilitation program can significantly improve a patient's physical and psychological function. These programs usually involve both pulmonary and whole body rehabilitation and use a multidisciplinary team composed of occupational and physical therapists, respiratory therapists, psychologists, speech therapists, nutritionists, nurses, social workers, and physicians working collaboratively with patients and their families to reach jointly declared rehabilitative goals. The impact of such units on the outcome and cost of care for patients receiving prolonged ventilation is currently being examined in the Chronic Ventilator Demonstration Project conducted by the Health Care Financing Administration.[38] Preliminary data from one of the four sites involved in this project suggest that a significant improvement in patient's physiological and psychological state is obtained when ventilator-dependent patients are enrolled in such treatment programs.[39]

As participants in the Chronic Ventilator Demonstration Project, we have studied the effects of a comprehensive multidisciplinary rehabilitation program on cognitive function and affective disorders in patients receiving prolonged ventilation treated in a noninvasive respiratory care unit. As shown in Figure 3, patients and their families reported an overall reduction in cognitive problems when treated in the ventilator stepdown unit (VSDU) using specific strategies to minimize disorientation and compensate for memory lapses. Patients in the VSDU were provided with clocks and calendars to maintain orientation and were actively encouraged to perform as many activities of daily living as possible. Ongoing psychological support was used to enhance patient's weaning success in order to reduce emotional stress—by providing encouragement to participate maximally and counseling when needed to address adjustment problems. In addition, steps were taken to decrease noise and to avoid unnecessary nocturnal interventions.

Despite the need for long-term ventilator support, patient mobility is required to facilitate whole body rehabilitation and to maintain maximal functional status. Secondary to recent advances in medical technology, patient mobility is enhanced by using portable ventilators as much as possible. In our unit, patients receive mechanical ventilation predominately via portable volume ventilators that provide patient mobility by liberating patients from large stationary ventilators and permit patient ambulation and out-of-hospital activities to enhance a sense of independence and limit feelings of isolation. Preliminary data from multidisciplinary treatment programs for long-term ventilated patients, such as ours, suggest that a significant improvement in patient functional status is obtained when they are treated in such multidisciplinary treatment programs.

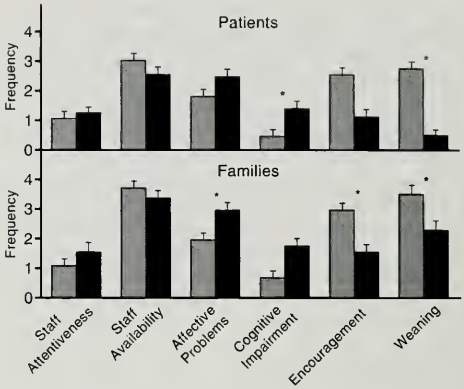

Fig. 3. The perceptions of patients and families of care given in the Ventilator Step Down Unit (VSDU) compared to the ICU setting. A 5-point scale was used to rate each item corresponding to how the patient or family member rated the perceived feelings: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, 4 = very often (reprinted from Reference 39a).

Psychologic Treatments To Facilitate Weaning

Psychotropic Medications

Several studies have attempted to reduce dyspnea and improve exercise capacity in COPD patients by employing a range of psychotropic medications, which includes diazepam,[40] alprazolam,[41,42] promethazine,[43] dihydrocodeine,[44] and morphine.[45,46] Although the beneficial effects of the benzodiazepines are contradictory and limited, the administration of opiates has been significantly associated with reduced breathlessness and improved exercise tolerance when examined in studies conducted in a small number of patients. Light and colleagues[45] reported that 13 eucapnic COPD patients (FEV_1 = 0.99 ± 0.48 L) increased maximal workload by 18% and oxygen consumption by 19% after ingesting oral morphine (0.8 mg/kg) compared to baseline. Following morphine ingestion at end exercise, mean ISD P_{aO_2} was lower (66 ± 12 torr vs 72 torr) and P_{aCO_2} was higher (44 ± 8 torr vs 38 ± 8.5 torr). Despite a higher level of ventilation achieved at ex-

haustion following morphine ingestion, the sensation of dyspnea was similar to the control condition. Although the exact mechanism(s) responsible for the improvements in breathlessness and exercise capacity following opiate administration are not known exactly, several hypotheses have been proposed, such as reduction in ventilatory drive,[46] reduction in central perception of breathlessness,[45] and a reduction in VO_2 at any given workload.[47] Although opiate administration may have a beneficial effect on improved exercise capacity and reduced breathlessness, its use in facilitating weaning in ventilator-dependent patients is limited because of its side effects of sedation and hypercapnia. However, recent studies by Young and colleagues[48] have demonstrated that low-dose nebulized morphine also reduces the perception of breathlessness but avoids the adverse effects of sedation and hypercapnia. At the present time, however, the routine use of opiates to facilitate weaning from mechanical ventilator support cannot be advocated, and its use is mainly relegated to the improvement of breathlessness in terminal patients receiving mechanical ventilation.

Biofeedback Training

Previous studies[49, 50] have reported the use of biofeedback training and/or relaxation techniques to reduce the sensation of breathlessness and anxiety in asthmatics. The process of biofeedback encourages the subject to control physiologic responses (heart rate, respiratory rate, muscle contraction, anxiety) by using relaxation techniques while simultaneously monitoring visual and auditory signals to achieve the targeted training goals. Several recent studies have looked at the effects of biofeedback training or relaxation techniques to reduce anxiety and facilitate weaning from mechanical ventilation.

In 1979, Corson and colleagues[51] used visual biofeedback of tidal volume and respiratory rate measured by a pneumotachograph placed in the breathing circuit and displayed on an oscilloscope to wean 2 paralyzed ventilated patients over a period of 3 months. The visual signals of tidal volume and respiratory rate were used as targets by the patient to slow their respiratory rate and increase their tidal volume. They used 40-minute training sessions each day, 3-4 times/week. During a 3-month period, the 2 patients, who suffered from neuromuscular diseases and severe respiratory muscle weakness, were successfully weaned from ventilator support. Similar results were reported by LaRiccia et al[52] who used biofeedback from chest-wall movements obtained by two magnetometers to wean a multiple sclerosis patient who had failed several previous attempts to wean from ventilator support.

In a recent, prospective, randomized, controlled study, Holliday and Hyers[53] used biofeedback to improve weaning outcomes in 40 patients who had received ventilator support for 7 days or more. Patients randomly received biofeedback training using visual and auditory signals from rib-cage- and abdominal-compartment changes during tidal breathing measured by impedance plethysmography. A visual signal of frontalis muscle electromyographic (EMG) activity was used to enhance muscle relaxation and control anxiety (Fig. 4). Patients randomized to the biofeedback group trained for 15-30 min/day, 5 days/week until they were extubated. Patients receiving biofeedback training reported a significant reduction in anxiety and stated that they felt more relaxed during biofeedback sessions compared to the reports of the control group. Moreover, the biofeedback group showed a significant reduction in mean ventilator days compared to the control group that was associated with a significant increase in tidal volume, mean inspiratory flow, and V_T/diaphragm EMG, a measure of respiratory muscle efficiency. Although these results are encouraging, broader application of this technique is probably limited because of the requirements for sophisticated equipment and data analysis. However, Yarnal and colleagues[54] have reported on the use of the numerical display of expired tidal volume and respiratory rate on the patient's ventilator face-board as a simpler and more accessible form of visual feedback to wean difficult patients. The validation of biofeedback training and of relaxation techniques in facilitating weaning from prolonged mechanical ventilation in a larger number of chronic ventilated patients awaits further investigation.

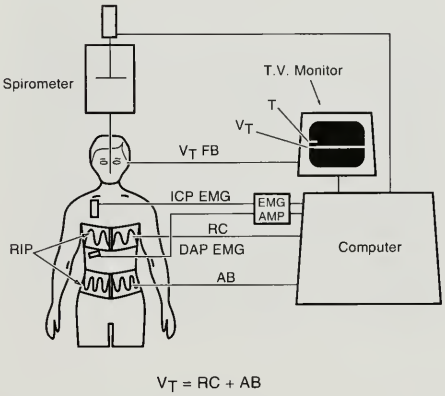

Fig. 4. Diagram of system described by Holliday and Hyers[53] to provide visual and auditory feedback to patients weaning from mechanical ventilation. Respiratory inductive plethsmograph (RIP) changes during breathing provide visual feedback of tidal volume (V_t FB). The display of frontalis muscle electromyograph (EMG) is used to control anxiety by muscle relaxation techniques. The measure of respiratory deficiency is derived by recording the diaphragm (DAP) EMG and relating that to displaced tidal volume (V_T/DAP). AB = abdominal; RC = rib cage; ICP = pectoralis EMG; T = threshold line. (Reprinted from Reference 53, with permission.)

Cold Facial Stimulation

Patients with extreme dyspnea due to a variety of underlying lung disorders note symptomatic relief when cool air is directed to the face from a fan or open window. Studies conducted in animals[55-57] and humans[58-60] have shown that airflow or cold solutions applied to the pharynx, nasal mucosa, or face may result in an alteration in breathing pattern[57] or reduction in total minute ventilation.[55-58] Schwartzstein and colleagues[61] studied the effect of 4°-10° C of cold air directed against the cheeks at 4 km/h on the sensation of dyspnea in 16 normal subjects breathing against elevated inspiratory loads while P_{aCO_2} was maintained at 55 torr. Cold air directed to the face produced a significant reduction in breathlessness, although, minute ventilation remained unchanged. Early investigators cited by Freedman[62] have shown that dyspnea is reduced even when air at ambient temperature is directed across the face during loaded breathing. The mechanisms responsible for the relief of breathlessness when airflow is directed across the face remain unclear but may include a decrease in minute ventilation, elicitation of the diving response, or stimulation of the trigeminal nerve. Whatever the responsible mechanism, however, the utility of this inexpensive modality for relieving dyspnea in the ventilator-dependent patient deserves further investigation.

In Conclusion

The clinical course of patients receiving long-term ventilator support may frequently be complicated by the development of psychological problems. We believe that treatment plans that focus on isolating the cause of psychological disorders in a comprehensive biopsychosocial approach have the best chance of improving the patient's functional status and facilitating the successful withdrawal of ventilator support. Newer approaches that foster the independence of patients, decrease isolation, and restore their control over their own destiny, such as comprehensive ventilator-dependent rehabilitation programs and respiratory biofeedback training may become important treatment options in the future but deserve further investigation at the present time.

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Tracheobronchial Fracture from Blunt Chest Trauma: A Case Report

Kenneth E Noblett MA RRT and Jeffrey W Selby MD

Introduction

Tracheobronchial fracture is a serious condition occurring in less than 3% of victims of clinically important chest trauma.[1] In the past mortality has been reported as high as 30%;[2] however, in recent years mortality has declined markedly, doubtless due to improvements in emergency care, life-support systems, and surgical techniques. This type of injury from blunt chest trauma can present some challenging diagnostic problems. Because of the infrequency and possible difficulty in early recognition, this condition may not become apparent until the subsequent onset of pulmonary problems. We present the case of a traumatic tracheobronchial fracture with a delayed clinical manifestation.

Case Study

A 35-year-old man presented to the emergency department with pain in the right side of his chest and severe shortness of breath. Examination revealed respiratory rate 34 breaths/min; heart rate 100 beats/min; blood pressure 132/88 mm Hg; arterial blood gas values pH 7.45; P_{CO_2} 31 torr; P_{O_2} 47 torr on oxygen at 5 L/min by nasal cannula. His electrocardiogram was normal but his chest radiograph revealed complete opacification of the right lung with marked loss of volume in the right hemithorax and shift of the mediastinum to the right. The left lung appeared normal (Fig. 1). Breath sounds were greatly diminished on the right but clear on the left. The patient was placed on oxygen at 10 L/min via a nonrebreathing mask. His pulse oximetry saturation (S_{pO_2}) rose to 85-90%, and his dyspnea improved markedly.

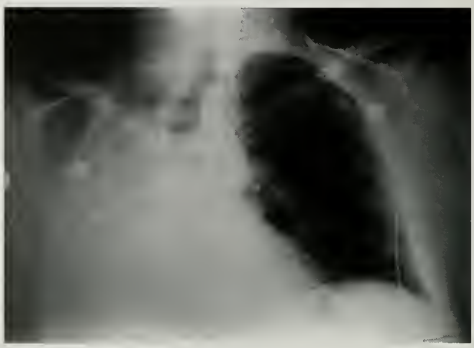

Fig. 1. Chest radiograph (anteroposterior) of a 35-year-old man on presentation to the emergency department with pain in the right chest and severe dyspnea. The film demonstrates almost complete volume loss in the right lung, with marked tracheal shift toward the right.

The patient had been hospitalized 6 weeks earlier following a motorcycle accident in which he sustained extensive subcutaneous emphysema, bilateral pneumothoraces, pneumomediastinum, bilateral pulmonary contusions, fracture of the second rib on the left and possible fracture of the first and second ribs on the right, laceration of the tongue, contusion of the left periorbital area, and abrasions of the knees. He was treated with bilateral chest tubes, rest, pain control, and prophylactic antibiotics but did not require mechanical ventilatory support. He was released from the hospital after 7 days and had been doing well at home until his current symptoms began and increased over the 24 hours prior to his current hospitalization. He had been increasing his exercise level and, in fact, had walked 3 miles the day before his admission!

The patient underwent flexible bronchoscopy shortly after this second admission, which revealed that the right main bronchus was more than 99% obstructed from what appeared to be scar formation, probably at the site of a bronchial injury (Fig. 2).

The patient was treated with ceftriaxone sodium (1 g I.V.) for possible pneumonia distal to the obstruction. Purulent se-

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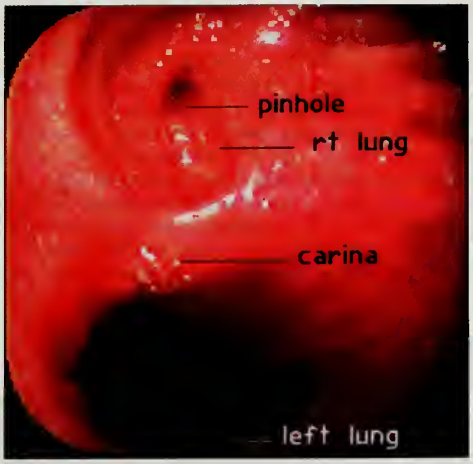

Fig. 2. Image(s) obtained during bronchoscopy shortly following admission. Image(s) reveal almost complete stenosis of the right mainstem bronchus.

cretions were noted during bronchoscopy, and pneumonia was confirmed when *Staphylococcus aureus* was grown from the bronchial washing.

After 3 days of antibiotic treatment to allow infection and inflammation to subside, the patient underwent a right thoracotomy, with resection of the bronchial stenosis and anastomosis of the right main-stem bronchus to the trachea. The patient tolerated the surgical procedure well and required no mechanical ventilatory support following surgery. He underwent daily bronchoscopies for the next 5 days for secretion clearance and was discharged 2 days later with no apparent complications. A follow-up bronchoscopy performed approximately 10 weeks following surgery revealed dramatic improvement in the lumen of the right main bronchus, which appeared essentially normal (Fig. 3).

Discussion

Tracheobronchial fracture is one of the rarer injuries associated with blunt thoracic trauma. Early diagnosis is important for optimal management of this life-threatening condition. Failure to diagnose can lead not only to higher mortality but also to delayed complications that may require extensive intervention.

Presentation

The rarity of tracheobronchial injuries is well documented although an apparent increase in occurrence may be attributed to increases in high-speed travel[3,4] or perhaps to a higher survival rate among victims of more serious trauma as a consequence of effective early treatment. It will be interesting to see what impact recent developments in passenger restraint systems (ie, mandated seat belt compliance and air bags) will have on the occurrence of major chest trauma.

Although the exact mechanism of tracheobronchial fracture is unknown several possible mechanisms may cause this injury. First, with blunt trauma there can be a flattening of the thorax and a widening of the transverse diameter and because the lungs 'follow' the chest wall, a 'pulling apart' may occur at the carina. Second, if the glottis is closed at the moment of impact and the trachea and major airways are trapped between the sternum and vertebral column, the sudden buildup of intrabronchial pressure can result in bronchial rupture. Third, during the rapid deceleration that occurs during blunt chest trauma, shearing forces may be exerted at points of fixation, namely the carina and cricoid cartilage.[5-8] Some combination of these factors is probably involved in the development of tracheobronchial fracture.

About 80% of such injuries involve the bronchi. The injury is usually parallel to the cartilage rings, occurring within 2 cm of the carina. The right side is affected more often than the left, but pulmonary vessels are rarely damaged.[6] The patient in our case report fits this pattern.

The patient with tracheobronchial fracture may present with a variety of symptoms, but in some instances few, if any, signs or symptoms are present. This latter condition makes early diagnosis difficult, and early diagnosis can be critical to a good patient outcome. A review of the literature reveals

Fig. 3. Image(s) obtained during bronchoscopy approximately 12 weeks following surgical repair of bronchial stenosis resulting from tracheobronchial fracture received during blunt chest trauma. Image(s) reveal an essentially normal right mainstem bronchus.

the primary findings to include cervico-mediastinal emphysema and/or generalized subcutaneous emphysema, pneumothorax, acute dyspnea, hemoptysis, sternal tenderness, and the Hamman's sign (a crushing sound with each heartbeat, heard on auscultation).[3,5,6,8]

Two findings should cause one to suspect tracheobronchial injury. If the patient requires positive pressure ventilation, not only will there be a pneumothorax (in the presence of open communication of the airway with the pleura) but massive generalized subcutaneous emphysema is also likely. These conditions persist and even increase despite the placement of a chest tube(s).[5-7]

The second important observation involves patients who do not require positive pressure ventilation. Such patients, with either an airway that is in open communication with the pleura or an airway that has some of its tissues intact, will develop mediastinal and deep cervical emphysema—conditions that may persist and even increase until the damaged airway has had time to seal, which may occur in as early as 1 week after the injury.[9] The first finding would make itself known in the early stages of patient stabilization; the second is somewhat more subtle and may be overlooked.

Diagnosis

Delay in diagnosis can be detrimental, even fatal, and complications from delay include atelectasis, empyema, hilar abscess, pneumonia, mediastinitis, sepsis, and possible multisystem organ failure.[7] Delayed diagnosis can produce one of two likely clinical courses depending on the extent of the injury to the airway. With a partial laceration of the airway, the normal healing process can produce stricture that can vary in the extent of lumen reduction produced. Recurring atelectasis, infection, and bronchiectasis can result with possible irreversible parenchymal damage being the final result, a consequence of the fibrosis that results from long standing atelectasis and/or chronic infection.[6,10]

If the injury results in a complete transection of the airway, then as each end of the severed airway heals hypertrophic granulation tissue can completely seal the airway lumen. This results in complete atelectasis of the lung distal to the injury site. If the stricture occurs quickly and completely there is little chance for infection, but absorption atelectasis quickly ensues.[7] Although there was some infection noted in our subject, the speed at which complete atelectasis occurred and the extent of the airway stricture lead us to believe that our patient suffered complete obstruction.

The primary diagnostic tools involved are the history, physical examination, a high index of suspicion, chest radiographs, and bronchoscopy. The chest radiograph is important because it is usually obtained early in the patient's presentation to the hospital. Radiographic findings with tracheobronchial fracture can include pneumothorax, bilateral pneumothoraces, pneumomediastinum, rib fractures, clavicle fractures, pneumopericardium, and widened mediastinum.[7] Because of the sometimes occult nature and varied presentation of tracheobronchial fracture, several attempts have been made to find a focal injury that might serve as the primary diagnostic indicator of tracheobronchial fracture.

One of the primary findings that would cause one to suspect tracheobronchial fracture is a pneumothorax,[7] especially one that does not respond to chest tube evacuation.[6] In fact, application of suction to the chest tube may actually increase the air leak and the patient's respiratory distress. The increased distress can be attributed to evacuation of air that, prior to the application of suction, was involved in gas exchange.[10] Another abnormality once thought to be a primary indicator is the presence of fractures involving the first three ribs, however, later research seems to show that this cannot be a definite diagnostic indicator.[11] However, one does have to suspect that the chest has been subjected to a great amount of blunt force for fractures involving the first three ribs and/or clavicle to result. The patient in our case did fit this pattern, with fracture of the first rib on the right and the second ribs bilaterally.

Although these abnormalities may suggest airway damage, two findings have been suggested as reliable indicators of airway injury—first, abnormalities in the appearance of the endotracheal tube, either an overdistention of the cuff or extraluminal position of the tip, and second, the findings of the "fallen lung sign," which is the collapse of the lung toward the lateral chest wall.[12] Both of these radiographic findings may be rare; yet, they stand as important observations that can easily be overlooked or forgotten.

The difficulty in making the diagnosis of bronchial injury is well documented. Burke[2] in an early review of 167 cases found that 68% of these patients were stabilized from their trauma but did, in fact, have airway injury. Burke observed

> These trivial, observable injuries and the initially satisfactory response to treatment give no clue to bronchial injury and no further diagnostic efforts are made. The patient is peacefully allowed to develop a bronchial stricture with all of its hazards.

It has been reported that about 10% of patients with tracheobronchial fracture have no radiographic or physical findings, which adds to the difficulty in making an early diagnosis. This absence of findings is probably the result of the bronchial sheath's remaining intact; thus, air does not enter the pleura or mediastinum.[13] A delayed diagnosis is made after the late onset of pulmonary problems due to bronchial stenosis—reported from 1 month up to 32 years following the trauma.[2] It remains extremely important that an early diagnosis be made. Although repair is possible at a later date, a delay in diagnosis may result in a serious loss of functioning lung tissue.[2,7]

The most effective procedure to confirm a diagnosis re-

mains direct visualization of the tracheobronchial tree via flexible or rigid bronchoscopy.[3,5-8,10] While all agree that bronchoscopy is the best procedure for diagnosis of tracheobronchial fracture, two problems are noteworthy. First, is answering the question,Who needs to have the procedure done? The second is the many cases of the injury that may be missed during bronchoscopy.

There are no specific criteria for determining who receives a bronchoscopic examination following blunt chest trauma. Hara and Prakash[14] have evaluated the value of fiberoptic bronchoscopy within the first 3 days following acute chest trauma. They established that routine early fiberoptic bronchoscopy is useful in the evaluation and diagnosis of 53% of patients involved in acute blunt trauma to the chest.[14] The usefulness of bronchoscopy in this classification of patients has been confirmed by several clinician-authors;[4-7] yet, the decision to perform bronchoscopy ultimately relies on the clinical judgment and experience of the physician. A review of the literature reveals several reasonable indicators that suggest consideration of bronchoscopy in the patient following blunt chest trauma (Table 1).

Table 1. Indicators for Bronchoscopy following Blunt Trauma to the Chest.

Primary
Subcutaneous emphysema:
1. Generalized (massive amounts during positive pressure ventilation)
2. Generally confined to the medial anterior chest and cervical areas (especially when not subjected to positive pressure ventilation)
Pneumothorax:
1. Pneumothorax that poorly responds to chest-tube placement
2. Pneumothorax with which the patient gets more dyspneic when suction is applied to the pleural space
3. Pneumothorax with which the "air leak" increases when suction is applied or increased within the pleural space
'Fallen lung' sign on chest radiograph
Endotracheal-tube abnormalities on chest radiograph
Overdistention of the cuff
Extraluminal position of the tip
Sternal tenderness
Pneumomediastinum on chest radiograph
Hemoptysis
Hamman's sign
Secondary
Clavicle fracture
Rib fracture(s)
Pulmonary contusion

We believe these reasonable indicators, based on clinical findings could be helpful in establishing who needs early bronchoscopy following chest trauma.

The second problem encountered is complex and difficult to verify. Baumgartner et al[7] showed that even when bronchoscopy is carried out there is a significant correlation between the skill and experience of the endoscopists and actually finding the injury under direct visualization. Repeat bronchoscopies may be indicated in this patient population especially if clinical symptoms persist.[7,14] Therefore, although bronchoscopy is a mainstay for proper diagnosis, it is not foolproof.

Management

Whether the tracheobronchial fracture is found early or late, the treatment involves surgical repair. Since the first reported successful surgical repair in 1948,[2] numerous advances in the surgical techniques for repair of tracheobronchial fracture have been made. Reports indicate that early repair produces good long-term results and preservation of lung function in about 90% of the cases undergoing surgery.[10] In most cases the site of the injury establishes the surgical intervention plan of action. Injuries involving the trachea require urgent restoration. Injury to the mainstem bronchi can be done in a somewhat more conservative manner, mainly via resection. If onset of signs and symptoms and diagnosis are delayed, disinfection of the tracheobronchial tree may be needed. If the injury involves the smaller airways, treatment may involve resection or laser repair.[4]

One of the most important measures is airway control during or prior to surgical intervention. If the injury is in the trachea, it is imperative that tracheal intubation be done distal to the injury preferably under direct visualization via bronchoscopy. If the injury involves a bronchus, intubation with a dual-lumen tube may be indicated; however, a single-lumen tube may be preferable when the main bronchus of the unaffected lung is to be intubated. This may allow more freedom for surgical repair of the injured airway. When the affected lung needs to be ventilated during the surgical procedure, high-frequency ventilation may be very useful. By placing the tip of the orotracheal tube cephalad to the injury and the tip of the gas inflow catheter distal to the injury site, gas exchange can take place in the affected lung. This method of ventilation also allows for a less obstructed field during the surgical repair.[3]

In Summary

Although tracheobronchial fracture is rare, detection or exclusion require careful diagnosis under the sometimes adverse conditions surrounding the trauma patient. The injury can be treated effectively especially when an early diagnosis is made. Our case had an ultimately excellent outcome, but it suggests one possible scenario following tracheobronchial fracture. Those who treat victims of blunt chest trauma are urged not to forget about this sometimes elusive and dangerous injury.

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FACE TO FACE WITH CHANGE

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Selective Drug Therapy for Pulmonary Hypertension

Hugh S Mathewson MD

Introduction

The pathogenesis of pulmonary hypertension can be obvious, as it is in hypoxemic states, or obscure, as is the case with primary pulmonary hypertension. Decreased airway P_{O_2} is the main stimulus for hypoxic pulmonary vasoconstriction, which is presumed to be an autoregulatory mechanism for maintenance of optimal ventilation-perfusion ratios. Although the physiologic basis of this mechanism is unknown, the obvious vasodilator drug is oxygen, which exerts a marked preferential effect on the pulmonary vasculature in the presence of hypoxemia. Restoration of a normal airway P_{O_2} is usually the sole therapeutic requirement for relieving hypoxic pulmonary hypertension, although oxygen may in some instances fail to improve cardiac output.

There are other conditions, however, in which pulmonary hypertension is not directly caused by hypoxemia. Intracardiac defects with residual left-to-right shunts comprise the major causes of precapillary pulmonary hypertension. Postcapillary causes include left ventricular failure, mitral stenosis, and obstructive conditions of the pulmonary venous system. Often these disorders are amenable to drug therapy (eg, inotropic agents) or to surgical correction. Management of patients with operable defects may include vasodilator administration for diagnostic purposes or to relieve pulmonary vasoconstriction in the perioperative period.

The foregoing comprise about 95% of conditions causing pulmonary hypertension, indicating that increased pulmonary vascular resistance (PVR) is nearly always secondary to underlying respiratory or cardiovascular disease. Primary disease of the pulmonary vasculature can be due to veno-occlusive disease or chronic thrombotic obstruction or may constitute a diagnostic entity known as primary pulmonary hypertension (PPH). Because there is no specific identifying test for PPH this is a diagnosis made by exclusion when all secondary causes of pulmonary hypertension have been ruled out.[1,2] The principal lesion in PPH is an obliterating vasculitis, which is progressive in most cases. The expected time of survival of patients with PPH has, until recently, been less than 5 years.

Certain varieties of pulmonary hypertension are confined to newborns. Persistent pulmonary hypertension[3,4] is a neonatal disorder in which there is a continuation of the fetal circulatory condition, with pulmonary vasoconstriction and a marked curtailment of pulmonary blood flow. Blood is shunted from right to left, either through the foramen ovale or the ductus arteriosus, producing venous admixture sufficient to cause profound tissue hypoxia. The pathogenesis is obscure, but on postmortem examination many infants have shown abnormal muscular hypertrophy of the pulmonary arterial walls. Congenital diaphragmatic hernia is commonly associated with this condition. A stressed newborn may revert to a fetal-type circulation, especially if he has a low-birthweight or shortened gestational age. An effective pulmonary vasodilator may preserve blood flow to the lungs until the cause of the stress is relieved.

The principal goal of treatment in all cases is preservation of right ventricular (RV) function, that is, to reduce afterload to RV ejection. The RV is a relatively thin-walled, highly compliant and distensible structure. Unlike the left ventricle, which usually is able to withstand marked rises in afterload, even small increases in RV afterload cause significant reduction in stroke volume. RV output is usually maintained up to a mean pulmonary artery pressure of about 40 mm Hg.[5]

Vasodilator drugs usually affect both the systemic and pulmonic vasculature. In the past, attempts have been made to treat pulmonary hypertension with sodium nitroprusside or nitroglycerin. Although both are potent pulmonary vasodilators, the concomitant decrease in systemic arterial pressure seriously limits their clinical usefulness. Similar experiences have been reported with hydralazine and with the alpha-adrenergic blocking agents tolazoline and phentolamine.

Drug Mechanisms

Current research is directed toward the development of drugs that are specific vasodilators of the pulmonary vasculature. Two physiologic mechanisms are targeted. The first is the receptor-coupled adenylate cyclase system. This is the major mechanism by which β-adrenergic catecholamines (epinephrine, iso-

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proterenol) accomplish both bronchiolar and arteriolar relaxation. Occupancy of the receptor coupled to adenylate cyclase leads to the production of cyclic adenosine monophosphate (cAMP). The increased levels of cAMP activate a cAMP-dependent protein kinase that augments the phosphorylation of myosin and results in relaxation of vascular smooth muscle. Allied to this mechanism is the action on prostanoid receptors, which is linked to the adenylate cyclase system. Agents such as prostaglandin PGE_1 and prostacyclin (PGI_2) exert their vasodilator effects via this pathway.[6,7]

The second major mechanism is the guanylate cyclase pathway, leading to the formation of endothelium-derived relaxant factor (EDRF). Although this sequence is less well understood, it has been shown that activation of guanylate cyclase by EDRF or other nitroso-containing compounds leads to an increase in cyclic guanosine monophosphate (cGMP), activating a family of cGMP-dependent protein kinases, which presumably cause phosphorylation of myosin as part of the relaxant process.[8] It has been established that nitric oxide appears to have activity identical to EDRF,[9] and that it is synthesized from *l*-arginine in endothelial cells.[10]

Nitric Oxide

Nitric oxide (NO) is an unstable, highly reactive gas characterized chemically as a free radical. Its pulmonary specificity is entirely due to its pharmacokinetics.[11] When given by inhalation in concentrations of 20-40 ppm, it diffuses rapidly through the alveolocapillary membrane and exerts its relaxant effect on the pulmonary vasculature. Then it is immediately bound to the circulating hemoglobin, forming nitrosyl-hemoglobin that is then rapidly oxidized to methemoglobin. The removal is virtually quantitative, so that practically none of the inhaled NO reaches the systemic circulation.[12] The nitrosyl residue is oxidized to form nitrite and nitrate.[13]

Studies have shown that endogenous NO is an important modulator of perinatal pulmonary vascular tone.[14] Newborns with persistent pulmonary hypertension,[3,4] and pediatric patients with congenital heart disease and pulmonary hypertension[15] react favorably to NO, with prompt reduction of pulmonary artery pressure. Similar responses have also been demonstrated in adults with PPH[16] and in those with mitral valve disease.[17] Of particular interest is the potential for improving gas exchange in patients with severe acute respiratory distress syndrome (ARDS).[18-22] Improvement in oxygenation occurs because the inhaled NO is distributed according to ventilation; thus, the associated vasodilatation increases blood flow to well-ventilated alveoli. In addition, inhaled NO may, to a limited extent, relieve bronchoconstriction.[23]

There are obvious limitations to the therapeutic use of NO.[24] Its preparation, storage, and delivery present technical problems that can be difficult and expensive. Because its effective half-life is only a few seconds, administration must be continuous, and the obtainable benefits are temporary. Also there is considerable toxic potential associated with the high reactivity of the gas.[25] In addition to the destruction of hemoglobin, there also is production of nitrogen dioxide (NO_2)—a potent alveolar irritant.[13] Inhaled concentrations must be accurately metered; up to 80 ppm have been employed, but this approaches the limit of human tolerance. For perinatal and perioperative pulmonary hypertensive crises, NO has established applicability,[26] but its use will continue to be confined to well-monitored operating rooms and critical care units.[27,28]

Current Treatment of PPH

This uncommon but serious illness is the subject of a review in the February 1994 Supplement to *Chest*.[29] The main features of the pathogenesis, including genetic factors, are summarized,[1,30,31] and methods of treatment reviewed.[32,33] The series presents separate reports of more than 100 cases each from France,[34] the United States,[2] and the United Kingdom[35] with their respective therapeutic regimens and clinical outcomes. Two components of drug treatment appear to be well established: the use of anticoagulants and the administration of large doses of calcium-channel blockers.[36] Of the anticoagulant agents, warfarin is the most widely used, although it is suggested that heparin, given its inhibitory effects on smooth-muscle-cell proliferation, might be more suitable.[32]

Pulmonary vasodilatation has been successfully achieved with calcium-channel blockers in high dosage, such as 720 mg of diltiazem or 240 mg of nifedipine daily.[36] The risks of systemic cardiovascular depression are obvious, and the drugs must be titrated to effect with careful hemodynamic monitoring. Several new calcium-channel blockers that have more selective vascular effects and are less negatively inotropic[32] are under investigation.

Surgical interventions, such as atrial septostomy and, in extreme cases, heart-lung transplantation, are also evaluated in the *Chest* supplement.[29] An international registry has recently been organized that is expected to monitor PPH patients with greater accuracy, particularly with emphasis on the outcomes of drug trials.[37]

Prostacyclin (PGI_2)

Extensive use of this agent in Europe, both for diagnosis and therapy, has demonstrated its efficacy as a pulmonary vasodilator.[7] Prostacyclin is an eicosanoid, a 20-carbon atom lipoidal compound that is an arachidonic acid metabolite. It is a potent vasodilator with a half-life of about 5 minutes. It is commonly employed (in Europe) to assess the vasodilatory capacity of the pulmonary vasculature. Given intravenously by infusion at rates of 2 to 4 $ng \cdot kg^{-1} \cdot min^{-1}$ it can be useful in predicting response to long-term vasodilator therapy.[38] It may prove to be especially effective in controlling pulmonary vascular

resistance during and after some surgical procedures for congenital heart disease.[39,40] Continuous PGI_2 infusions have been shown to improve exercise tolerance and decrease symptoms in patients with PPH.[41,42] Side actions are common, including headache, flushing, and hypotension. Prostacyclin is not yet available for clinical use in the United States, but its release is anticipated.

Iloprost

Prostacyclin must be given intravenously; it is relatively unstable and must be protected from light. Its solutions lose their efficacy if allowed to stand for more than 12 hours. Iloprost, a synthetic analogue of PGI_2, has an approximate half-life of 13 min.[43] It can be stored at room temperature and has an oral bioavailability of 13%, indicating that an oral preparation could be developed. Preliminary reports on the use of iloprost for treatment of PPH have been favorable.[44]

Adenosine

It is not surprising that adenosine, a component of the cAMP molecule, has smooth-muscle-relaxant properties. Some evidence suggests that it exerts a preferential vasodilator effect on the pulmonary circulation.[45] At least three papers report on its use for treatment of PPH.[45-47] In one of them, adenosine was combined with nifedipine, which reduced PVR by 49%.[46] Another investigation compared these two drugs, finding that adenosine reduced PVR but nifedipine did not.[47] All three studies found adenosine to be immediately beneficial. However, adenosine has a half-life of less than 10 minutes and must be given intravenously. It has potent negative inotropic, dromotropic, and chronotropic properties, and can cause pacemaker dysfunction, coronary steal, and systemic hypotension.[48] Its eventual applicability may be confined to administration for diagnostic purposes or in emergency situations pending corrective surgery.

Bipyridine Derivatives

The physiologic action of cAMP is limited by its almost immediate conversion to the inactive AMP. This is catalyzed by an intracellular enzyme called phosphodiesterase-fraction three (PDE-III). Inhibition of this enzyme prolongs the action of cAMP and extends the duration of smooth muscle relaxation. Theophylline and its derivatives are PDE-III inhibitors, although in ordinary dose ranges this effect is probably minor. Two bipyridine derivatives, amrinone and milrinone, are PDE-III inhibitors that have positive inotropic as well as vasodilator properties. Experimental data indicate that PDE-III inhibitors of this type cause the release of NO from the vascular endothelium.[49] Both amrinone and milrinone reduce PVR in animal models with pulmonary hypertension. In one study, milrinone substantially decreased pulmonary artery pressure without significant change in systemic arterial pressure.[50]

Two clinical studies of milrinone, employed for its inotropic effect in patients with congestive heart failure, showed that in addition to improving hemodynamics the drug significantly reduced PVR.[51,52] This is in marked contrast to the action of established inotropic agents such as dobutamine, which does not reduce right ventricular afterload.[53] Milrinone is currently under study in Europe as an agent to provide inotropic support to patients following open heart surgery.[54,55] A consistent finding is reduction of PVR in a population of patients that cannot withstand large changes in systemic hemodynamics.

Endothelin Antagonists

Much of the research on the pathophysiology of PPH has centered on endothelial dysfunction, which leads to intimal thickening and eventual obliteration of pulmonary arterioles. The respective roles of prostacyclin and NO have focused attention on endothelium-derived vasoactive metabolites. A group of such compounds are the endothelins, which are 21-amino acid peptides that exist in 3 known isoforms: ET-1, ET-2, and ET-3. It appears that ET-1 is one of the most powerful vasoconstrictors yet identified.[56] Antagonistic biochemical mechanisms between ET-1 and NO have been demonstrated in vascular endothelial cells.[57]

A cyclic neuropeptide (BE-18257B) has been isolated from *Streptomyces misakienesis*, which can displace ET-1 from the receptors on vascular smooth muscle and antagonize its pressor effects.[58] Vasoconstrictor antagonists of this type represent a new line of investigation in elucidating the nature of PPH and offer promising leads for therapy.

Conclusion

The vasodilator compounds now known are far from specific for the pulmonary vasculature, except for NO, which does not gain entry to the systemic circulation when administered by inhalation. From a broad spectrum of compounds, ranging from prostacyclin and other eicosanoids to calcium-channel blockers and PDE-III inhibitors, a drug with strong pulmonary and weak systemic vasodilator properties may yet appear. At this point, investigators express confidence that long-standing relief from pulmonary hypertension will soon be attainable with pharmacotherapy.

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FACE TO FACE WITH CHANGE

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Comparative Review of Respiratory Care Equipment Texts

Respiratory Care Equipment, edited by Richard D Branson, Dean R Hess, and Robert L Chatburn, with 19 contributors. Hardbound, 568 pages. Philadelphia: JB Lippincott, 1995. $49.95.

Principles and Applications of Cardiorespiratory Care Equipment, edited by David H Eubanks and Roger C Bone, with 14 contributors. Hardbound, 394 pages. Chicago: Mosby-Yearbook, 1994. $48.95.

Respiratory Care Equipment, 5th ed, by Steven P McPherson with a 5-member editorial-review board. Hardbound, 413 pages. Chicago: Mosby-Yearbook, 1995. $54.95.

Equipment Theory for Respiratory Care, by Gary C White. Hardbound, 505 pages. Albany: Delmar, 1995. $48.95.

For years, Steven McPherson's **Respiratory Therapy Equipment** has been a mainstay for respiratory care programs. This book has been joined in the market by others with similar content. The purpose of this review is to look at four respiratory therapy equipment texts descriptively and analytically with recommendations for authors as they consider future editions.

These texts cover the equipment commonly associated with respiratory care as it is practiced in most institutions (Table 1). McPherson does not cover hyperbaric oxygen, a therapy that is administered by many respiratory therapists; nor does McPherson cover blood gas electrodes and the aspects of quality control that now pervade all aspects of laboratory medicine. Eubanks and Bone fail to cover home-care and transport ventilators. Transport ventilators are not covered by White either, although many hospitals have adopted transport ventilators for good reason, as detailed in the text by Branson et al. Because the field has made significant inroads into home care, these ventilators are important. Perhaps, the Eubanks and Bone text intentionally covers only hospital-use equipment, leaving other authors to cover home-care equipment. Only White has omitted coverage of high-frequency ventilators, primarily applicable to neonates. The Eubanks and Bone text does not cover pediatric ventilators.

Table 1. Chapter Title and Content Comparison

Text	Branson, Hess & Chatburn	Eubanks & Bone	McPherson	White
Physical Principles of Gases	CH	PGS	CH	PGS
Compressed Gases and Piping Systems	CH	CH	CH	PGS
Gas Delivery Systems and Appliances	CH	CH	CH	PGS
Hyperbaric Oxygen	CH	PGS	NC	PGS
Humidifiers and Nebulizers	CH	CH	CH	CH
Airways and Suctioning	CH	CH	CH	CH with resuscitation
Resuscitation Equipment	CH	PGS	CH	CH with airways
Blood Gas Measuring	CH	PGS	NC	PGS
Noninvasive Respiratory Monitoring	CH	CH	CH	PGS
Flow and Volume Measuring (PFT)	CH	PGS	PGS	PGS
Airway Pressure Monitoring	CH	PGS	PGS	PGS
Intermittent Therapy Devices	CH	PGS	PGS	CH
Classification of Ventilators	CH	PGS	CH	PGS
Mechanical Ventilators	CH	PGS	CH (5)	PGS
Transport Ventilators	CH	NC	CH with homecare	NC
Home Ventilators	CH	NC	CH with transport	PGS
High-Frequency Ventilators	CH	CH	PGS	NC
Spontaneous Breathing Systems	CH	PGS	PGS	PGS
Expiratory Pressure Valves	CH	PGS	PGS	PGS
Decontamination	CH	NC	NC	NC
Computers	CH	PGS	NC	NC
Approval and Surveillance of Medical Devices	CH	PGS	NC	NC
Pediatric Ventilators	PGS	NC	CH	PGS

key: CH = entire chapter; PGS = content covered in pages within a chapter; NC = not covered in this book

Only Branson et al cover decontamination–critically important because practitioners are faced with the threats of human immunodeficiency virus (HIV), methicillin-resistant *Staphylococcus aureus* (MRSA), hepatitis-B infection, multiple drug-resistant tuberculosis, and diseases caused by other microorganisms. For several years, the National Board for Respiratory Care (NBRC) de-emphasized this topic in their examinations believing it to be an ancillary function. However, with cuts in staffing and the renewed attention to health-care workers' personal protection, decontamination of equipment has again become an important task for respiratory care practitioners.

McPherson and White do not cover the use of computers or the surveillance and approval of medical devices. It has become increasingly important for practitioners at all levels to know how computers work and how to use the software. Patient charting, departmental record keeping, and research are only three of the applications in which therapists are currently involved. Surveillance of medical devices encompasses quality control, which is important in the measurement of any variable. Approval of medical devices is of interest to those involved in clinical testing for manufacturers.

Each text has several special features designed to introduce the reader to chapter content and emphasize key points or formulas, including objectives and glossaries. Of particular interest to this reviewer is the extent to which the author/editors used contributors and references to the medical literature. These special features are listed in Table 2.

Table 2. Special Features of Each Text

Branson, Hess, & Chatburn	AARC Clinical Practice Guidelines; chapter outlines and objectives at the beginning of each chapter; a shaded box of key terms in each chapter; numerous shaded equation boxes; extensive referencing to the medical literature; a 9-page glossary; chapters on computer use and equipment approval; renowned contributors.
Eubanks & Bone	AARC Clinical Practice Guidelines; major section on unconventional ventilation (eg, high-frequency positive pressure ventilation [HFPPV] and high-frequency oscillation [HFO]); section on metabolic monitoring; major section on plethysmographs; emphasis on cardiopulmonary laboratory equipment; objectives at the beginning of each chapter, extensive information on extracorporeal membrane oxygenation (ECMO) and intravenous oxyenators (IVOX); extensive referencing to the medical literature; sections of suggested readings in some chapters; renowned contributors.
McPherson	Each chapter begins with a chapter outline, objectives, and key terms; shaded boxes emphasize key points; an 11-page glossary; a knowledgeable contributor.
White	Shaded boxes showing assembly and troubleshooting; self-assessment quizzes at the end of each chapter; introduction and objectives at the beginning of each chapter; a 9-page glossary.

Content Comparison

To make this comparison, I have chosen to look specifically at the chapter on aerosol and humidity devices and the discussion of the Puritan-Bennett 7200 ventilator, which are discussed in each of these texts.

Aerosol & Humidity

The Branson text uses the title, "Humidification: Humidifiers and Nebulizers." The chapter is 29 pages in length, with 63 illustrations and 61 references. Line drawings are sharp and instructive. By this I mean that the illustrations are of equipment currently in use or are generic and are clearly labeled, so the student can understand the piece of equipment when using the illustration and the written material (eg, Figs. 5-5 to 5-8). The photographs are usually clear, in that the purpose of control knobs is legible. Photographs are such that the product does not 'disappear' into the background. Several illustrations from the medical literature are provided to demonstrate current practices regarding the use of metered-dose inhalers, and three AARC Clinical Practice Guidelines are included. There is a particularly good, referenced table on artificial noses. Mist tents are not discussed. Otherwise, all the current equipment is more than adequately covered. I particularly like the emphasis on referring to the medical literature, rather than to equipment suppliers for performance and evaluation data. In general, the equipment is discussed in a generic sense, rather than as specific devices. This probably gives the book a longer applicable life because device names may change faster than the principles upon which the devices are based. The application of specific devices is left to the instructor. This is congruent with the NBRC examinations, which seldom mention brand names but rather emphasize the application of categories of devices.

The McPherson text uses the title, "Humidifiers and Nebulizers." The chapter is 33 pages in length, with 51 illustrations and 19 references. Line drawings are clear but not as instructive as in the text by Branson and colleagues (Figs. 4-6 and 4-7). Another example is that for the small particle aerosol generator (SPAG) (Fig. 5-57 in Branson et al versus Fig. 4-51 in McPherson). Many of the photographs are identical to those in Branson, Hess, and Chatburn, so, clarity is similar. McPherson does not cite the medical literature to the extent that Branson et al do. I question the need to discuss floating-island and centrifugal nebulizers, due to their obsolescence and the infection hazards involved.

The Eubanks and Bone text uses the title, "Humidity and Aerosols." It is 68 pages in length, with 74 illustrations and 163 references including those cited in the AARC Clinical Practice Guidelines. Line drawings are similar to those in the McPherson text. Photographs are generally clear so that the reader can determine the function of control knobs. This chapter combines the generic description with specific references to individual devices in some detail. For example, 10 different heated humidifiers are described. One unique feature is the section on aerosol particle scavenging and hospital personnel protection from aerosol particles.

The White text uses the title, "Humidity and Aerosol Therapy Equipment." It is 74 pages in length, with 44 illustrations and no reference to the medical literature; it does include 11 titles in a selected bibliography. Line drawings are similar to those in McPherson's book. The quality of the photographs makes it difficult to determine the function of control knobs; therefore, they are not very instructive. There is little in the way of generic description, but there are detailed descriptions of 6 heated humidifiers, mostly in terms of assembly and troubleshooting. A discussion of the Bird 500 mL micronebulizer may be unnecessary, as this device is probably obsolete. There is a discussion of the Devilbiss 65 ultrasonic nebulizer, but the unit pictured is not the Devilbiss 65 nebulizer, rather it is the Devilbiss 35 nebulizer,[1] a device that is rarely used. No discussion of metered-dose inhalers, aerosol spacer devices, or dry-powder inhalers is offered. This is a serious omission because these are some of the most common ways to administer inhaled medications. This chapter is basically a compilation of manufacturers' data and manuals.

Each of these chapters is well-organized. The differences are the emphases. The books by Eubanks and Bone and Branson and colleagues clearly emphasize aerosol therapy based upon the medical literature. The chapter in Eubanks and Bone includes extensive device-specific information. McPherson has an adequate generic description and a small number of examples. White is more device-specific and includes trouble-shooting sections for each device, but these tend to be repetitious among devices of the same type.

Puritan-Bennett 7200

The texts have adopted the Chatburn system of classifying ventilators, first published in RESPIRATORY CARE,[1] and all have included the same illustrations to present this classification scheme.

The text by Branson et al has a chapter entitled "Mechanical Ventilators," that begins with a table describing each of the ventilators detailed in the text (21 machines). The discussion of the 7200 is 6 pages in length and

includes 4 illustrations. One is a sharp, clear picture of the whole ventilator, ventilating a test lung. Two illustrations are excellent, clear line drawings of different configurations of the control panel. Students could easily determine the function of the control keys by viewing these drawings. This type of drawing is present for each of the ventilators in the text. The fourth illustration is a line drawing simplified from the actual internal schema. The text describes the ventilator's systems and operation, without going into the detail provided by the user's manual.

The McPherson text covers the 7200 in 5 pages with 3 illustrations. One illustration is of the ventilator, but it is not in operation and has no circuit attached. The next illustration is a poor quality photograph of the control panel, such that many of the control key functions are illegible; therefore, this illustration is not very instructive. The third illustration is a diagram furnished by Puritan-Bennett. Gas flow through the ventilator can easily be traced using the text, which adequately describes the operation of the ventilator. A shaded box lists the specifications of this, and each ventilator discussed.

The Eubanks and Bone text handles ventilators differently. Only a brief description is given of each ventilator, and then several tables of data for each ventilator are presented. The picture of the ventilator is of poor quality–not at all instructive. A 3-page table, that is basically copied from the manual, lists the specifications of the ventilator. The line drawings of the ventilator keyboard display panel are equally unintelligible and not instructive. One photograph of the actual keyboard is partially legible; the other is almost entirely illegible. No discussion or schema of the operation of the machine is provided. The information given is intermixed with information about several ventilators, which makes it very reader-unfriendly. I would not consider this treatment of the machine an adequate instructional tool.

The White text covers the ventilator in 14 pages. One noninstructive photograph shows the ventilator with a circuit attached; however, several other pieces of equipment are attached, making the picture too cluttered. The schema is the same as that in McPherson except it is larger, covering two adjacent pages. Tables of monitors and alarms are given, but the limits of the alarms are not listed. Apnea-monitoring parameters are listed in a separate table, with allowable ranges. A photograph of the exhalation filter is not instructive. An additional photograph of the inspiratory side filter is present, but probably unnecessary. No illustration of the control panel is provided. The drive system and control functions are adequately discussed.

Summary & Recommendations

The text by Branson, Hess, and Chatburn features excellent illustrations and is extensively referenced to the literature. The Eubanks and Bone text features good illustrations, excellent references, and detailed coverage of cardiopulmonary laboratory procedure; however, coverage of ventilators is disappointing. McPherson has good illustrations, fair referencing, and good coverage of ventilators. White is a basic text with adequate illustrations. It emphasizes assembly and troubleshooting but lacks references to the medical literature and has several key omissions and inaccuracies.

Regarding readability, the Branson et al, Eubanks and Bone, and McPherson texts are similar. As I reviewed the description of the ultrasonic nebulizer and the properties of particles, I could determine no difference in the style or readability. The White text tends to be somewhat more basic with terms such as frequency and amplitude defined and illustrated, as if to present these terms to individuals who were not familiar with them. The White text goes on to describe the same principles as the other texts using similar language.

The field of respiratory care is under considerable pressure from hospital administrators to become multiskill competent. Therefore, books that are broader in scope might be seen as contributing towards the goal of producing this multiskilled practitioner. According to the recent consensus conferences held by the American Association for Respiratory Care,[2] the role of respiratory care practitioners is expanding to include the use of equipment not addressed in these texts, such as instruments used to perform noninvasive cardiac monitoring: electrocardiography, echocardiography or doppler vasculography. Equipment for hemodynamic monitoring and measurement of cardiac output, either invasively or noninvasively, is not included except in a few pages in the book by Eubanks and Bone. Most educational programs are therefore forced to have students purchase a separate text for hemodynamic monitoring. Equipment for extracorporeal membrane oxygenation is mentioned only in Eubanks and Bone's book. Equipment for sleep laboratories (polysomnography) is mentioned on one page in Eubanks and Bone and is not covered in the other texts. Likewise, electroencephalography equipment is not covered. Cardiopulmonary laboratory personnel are increasingly responsible for assisting the bronchocopist with lavage, biopsy, and care of the bronchoscope. However, bronchoscopy is mentioned only in Eubanks and Bone's book. It has been suggested that intravenous-line insertion should be another role of the multiskilled therapist, a topic that none of these texts even mentions. Topics to cover should include intravenous solutions, types of lines, the many catheters inserted, and infusion pumps.

Perhaps, one of these authors should consider a "big book," similar to those edited by Barnes, Eubanks, Dantzker, or Scanlan, which are more comprehensive. Such a text would encompass equipment used by the therapist who has an 'expanded role,' as described by the AARC consensus conferences.[2]

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New Therapies for Neonatal Respiratory Failure edited by Bruce R Boynton, Waldemar A Carlo, and Alan H Jobe, with 42 contributors. Hardcover, 357 pages, illustrated. New York and Melbourne: Cambridge. 1994. $110.

During the past few years, neonatology has experienced a burgeoning of new techniques for the treatment of neonatal respiratory diseases. Five years ago, an understanding of intermittent mandatory ventilation was about all that was necessary to

manage neonatal respiratory failure. Now, those caring for infants must also know how to manage surfactant therapy, high-frequency ventilation, synchronized ventilation, and volume-cycled ventilation. In addition, intensive care professionals in many nurseries must also understand how to manage infants on extracorporeal membrane oxgenation (ECMO), nitric oxide, or negative-pressure ventilation. Modalities such as liquid ventilation have gone beyond laboratory curiosities and into the realm of clinical trials.

This book, **New Therapies for Neonatal Respiratory Failure**, fills an otherwise nearly empty niche by providing an overview of this rapidly changing field, while providing a sound physiologic basis upon which to build a deeper understanding of the techniques described. Drs Boynton, Carlo, and Jobe are superbly qualified to edit such a book because they have been intimately involved in various aspects of neonatal respiratory research for many years. All have contributed extensively to the book's content. Additionally, they have chosen an equally well-qualified group of individuals to contribute to the chapters, including Jeffrey Whitsett (Composition and Structure of Pulmonary Surfactant); Anne Greenough and Robert Chatburn (Advances in Conventional Mechanical Ventilation); Gregory Heldt and Graham Bernstein (Patient-Initiated Mechanical Ventilation); Thomas Shaffer, Jay Greenspan, and Marla Wolfson (Liquid Ventilation); and Billie Lou Short (Clinical Use of ECMO). Useful and interesting commentaries are added throughout by other noted researchers and clinicians in neonatology such as Mary Ellen Avery, Victor Chernick, and EOR Reynolds.

The text is divided into four parts. In Part I—Surfactant, chapters on surfactant structure, function, and metabolism precede an excellent review of the clinical trials and current use of surfactant by Roger Soll, T Allen Merritt, and Mikko Hallman. Future use of surfactant for abnormalities other than respiratory distress syndrome is addressed in the closing chapter of this section. In Part II—Mechanical Ventilation, the first chapters review respiratory physiology and mechanical ventilation and build a solid background for the following chapters about patient-initiated mechanical ventilation, high frequency ventilation, negative pressure ventilation, continuous flow oxygenation and ventilation, and liquid ventilation. Four chapters are dedicated to high-frequency ventilation and include a review of physiology and pertinent literature as well as practical, clinically oriented chapters on high-frequency oscillation, high-frequency flow interruption, and high-frequency jet ventilation. Part III includes two chapters on the theory and clinical use of ECMO. The book concludes in Part IV with a chapter on the physiology behind the current clinical interest in nitric oxide inhalation.

This book is not a primer; it requires a background in neonatal pulmonary care techniques and physiology. It is most valuable to physicians and neonatal caregivers who treat infants requiring these therapies or to those who plan to do so. For these professionals it is invaluable because it provides a review of pertinent physiology and literature in addition to providing in-depth information on the various modalities reviewed. It is a valuable teaching tool as well as a useful reference.

Most of this text is quite readable and illustrations are used amply. However, the editorial decision to reference works using authors and dates instead of reference numbers does interfere with readability, particularly when these references are placed mid-sentence [eg, "Collagen is not very distensible (Stromberg & Weiderhielm, 1969; Hoppin & Hildebrandt, 1977), but elastin is (Carton, Dainauskas, & Clark,1962).", page 97].

The chapter by Jose Venegas and Jeffrey Fredberg on oscillatory mechanics is elegant work but conceptually difficult. Not enough attention is paid to definition of terms and abbreviations; for example,

$$q = \frac{\sqrt{I/C}}{R_{aw}}$$

on page 194. The concept of q is not well explained, except in mathematical terms. Furthermore, by this time I had forgotten about the list of symbols and abbreviations in the front of the book, as previous chapters had defined all terms.

Despite these relatively minor problems, respiratory care practitioners who are actively involved in the care of neonatal patients requiring any of these new technologies should find this book of great value. Because neonatal respiratory care is rapidly changing, the editors of this book will need to revise and update this textbook frequently. Given the quality of this first edition, I certainly hope they choose to do so.

Sherry E Courtney MD MS
Associate Professor
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Division of Neonatology
Robert Wood Johnson School of Medicine
Cooper Hospital
Camden, New Jersey

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PRESCREENING SYSTEM. Nellcor Incorporated launches the new Healthquiz™ Prescreen™ system in Spanish. Now Spanish-speaking patients can give clinicians more accurate and complete information for preoperative assessments, according to Nellcor. The questionnaire can be tailored to match an organization's preoperative assessment forms and clinical protocols. The system uses a Healthquiz device with Prescreen software. Patients complete the questionnaire in Spanish by pushing a button to answer a series of 'si' or 'no' questions. The clinician can print a one-page summary report in English that highlights important health issues and calculates a risk score. The system can also suggest appropriate preoperative laboratory tests. In addition the Healthquiz device creates an electronic record for each patient's medical history and stores up to 125 histories on a small data card. A data application, PC Link, provides data management, custom reporting, and data integration. For more information, contact Nellcor Incorporated, Dept RC, 4280 Hacienda Drive, Pleasanton CA 94588, or call (800) NELLCOR. Please mention RESPIRATORY CARE.

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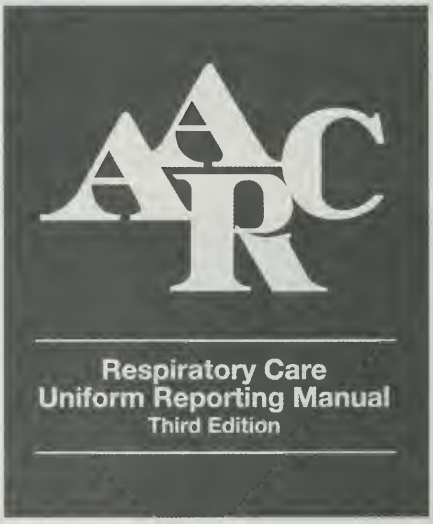

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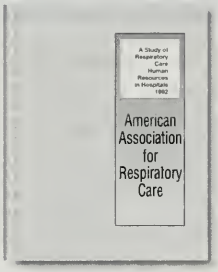

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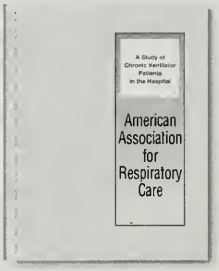

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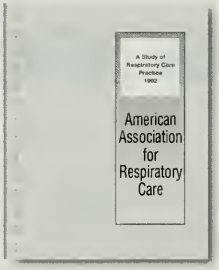

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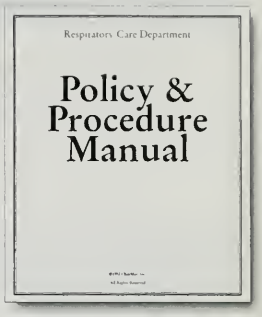

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- The grids for answers to questions, name, and AARC member number are found on the other side of this page. Using such grids enables a certain degree of automation and accuracy that would not otherwise be possible.
- This page is perforated to make it easy to complete and mail and to prevent tearing.

However, the rules of previous years apply.

- Only original Answer Sheets will be graded. No facsimiles or photocopies will be accepted. Six hours of CRCE credit is awarded to those who answer 35 or more questions correctly.
- You may photocopy the Answer Sheet for your personal record to check your answers against the Answer Key, which will be published in the October issue of RESPIRATORY CARE.
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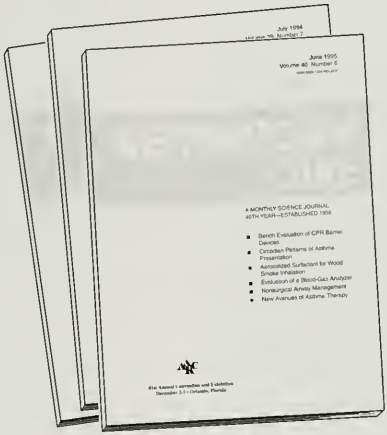
July 1994
June 1995
Volume 40 Number 6
A MONTHLY SCIENCE JOURNAL
40TH YEAR—ESTABLISHED 1956
Bench Evaluation of CPR Barrier Devices
Circadian Patterns of Asthma Presentation
Aerosolized Surfactant for Wood Smoke Inhalation
Evaluation of a Blood-Gas Analyzer
Nonsurgical Airway Management
New Avenues of Asthma Therapy

CRCE through the Journal–1995

We are delighted to bring you the sixth edition of ***CRCE through the Journal***, a program for AARC members to gain credit for continuing education derived from careful reading, thoughtful study, and test completion. The acceptance of these credits for the fulfillment of license-mandated continuing education is dictated solely by the licensure law of each individual state.

This year, we are indebted to the efforts of Crystal Dunlevy EdD RRT* and F Herbert Douce MS RRT who authored the test. This 50-item multiple-choice examination is based on papers published in RESPIRATORY CARE from July 1994 through June 1995. The issue and page numbers of the paper on which a question is based are shown in brackets following the question. You are free to consult the cited paper as you complete the answer sheet. However, we encourage you to read the paper in its entirety before answering the questions. Then, choose the single most-correct answer, and carefully mark the answer sheet. Remember ***CRCE through the Journal*** is an honor system, and the benefits you derive are directly proportional to the effort you invest.

Mail your completed answer sheet by September 30, 1995. Answer sheets postmarked after September 30 will not be processed. The Answer Key for ***CRCE through the Journal*** will be published in the October issue of RESPIRATORY CARE. No scores will be available from the AARC until the 1995 CRCE Transcripts are mailed in early 1996.

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* Dr Dunlevy is Associate Professor and Director of Clinical Education and Mr Douce is Assistant Professor and Program Director—The Ohio State University, Columbus, Ohio.

QUESTIONS:

1. In the respiratory care assessment-treatment program evaluated by Shrake and others, which of the following proved to be true?

   a. Overall utilization of respiratory therapy services increased.
   b. Cost-savings were reported only for the 3-month evaluation period.
   c. Cost savings were reported for both the 3-month evaluation period and for the 3-month period following the study.
   d. No significant cost-savings were reported.
   e. Patient care proved to be significantly improved.

   [July 94:715-724]

2. Which of the following findings reported by Palmisano and others is most likely to influence patient outcome during a cardiac arrest?

   a. variation in response times of individual members of the arrest team
   b. delay in providing epinephrine
   c. delay in administering oxygen
   d. delay in establishing intravenous access
   e. delay in activation of the cardiac-arrest paging system

   [July 94:725-729]

3. Acceptable indicators for bronchodilator therapy utilized by Wollam and colleagues include **all but which** of the following?

   a. $FEV_1 < 50\%$ predicted
   b. diagnosis of COPD or asthma
   c. previous use of corticosteroids or bronchodilators
   d. presence of auto-PEEP
   e. presence of wheezing

   [July 94:730-735]

4. Which of the following **was not** demonstrated in Padman and associates' case report of noninvasive positive-pressure ventilation for end-stage cystic fibrosis patients?

   a. improved oxygenation
   b. improved ventilation
   c. diminished sensation of dyspnea
   d. improved quality of life
   e. improved ability to perform daily activities

   [July 94:736-739]

5. According to Valeri et al, what factor influenced the compliance of mechanical ventilator breathing circuits after the first hour of use?

   a. type of plastic composition
   b. duration of use up to 48 hours
   c. circuit temperature up to 34°C
   d. flow setting on the ventilator
   e. No factor was found to be clinically important in influencing compliance.

   [August 94:793-796]

6. Which of the following aerosolized corticosteroids (when used on a chronic basis) has been associated with systemic side effects, including adrenal suppression?

   a. beclomethasone dipropionate
   b. triamcinolone acetonide
   c. betamethasone valerate
   d. budesonide
   e. dexamethasone sodium phosphate

   [August 94:837-840]

7. Who discovered penicillin?

   a. Pasteur
   b. Fleming
   c. Curie
   d. Salk
   e. LaVeque

   [August 94:850-852]

8. When administering albuterol via metered-dose inhaler (MDI) to an intubated, mechanically ventilated adult-lung model, which method delivers the largest amount of drug to the distal end of the endotracheal tube (ETT)?

   a. MDI directly attached to ETT between the Y-connector and the 15-mm adapter
   b. MDI attached to the inspiratory limb proximal to the Y-connector with the Aerochamber
   c. MDI attached to the inspiratory limb proximal to the Y-connector with the Aerosol Cloud Enhancer
   d. MDI attached to the inspiratory limb just distal to the humidifier
   e. MDI attached to the inspiratory limb just proximal to the humidifier

   [September 94:886-891]

9. Which of the following statements summarizes the findings of Jager, Tweeddale, and Holland regarding intubated COPD patients?

   a. Flow-triggered CPAP significantly reduced the work of breathing in this patient population.
   b. There was no difference in inspiratory work of breathing between flow-triggered CPAP and CPAP triggered by a preset pressure change.
   c. CPAP triggered by a preset pressure change significantly reduced the work of breathing in this patient population.
   d. Intubated COPD patients who are receiving sedation exhibited an increased work of breathing when flow-triggered CPAP was used.
   e. Inspiratory airway pressures were significantly lower in patients receiving CPAP triggered by a preset pressure change.

   [September 94:892-896]

10. For measurements of work of breathing, how does the Bicore CP-100 with updated software compare to conventional laboratory methods?

    a. Correlation coefficients and coefficients of determination are nearly equal and highly significant.
    b. Bias is excessive.
    c. Precision is unacceptable.
    d. Correlation coefficients are not statistically significantly different from zero.
    e. Reliability and validity are not acceptable.

    [September 94:897-905]

11. In the case report on unilateral lung disease chronicled by Schmitt, Mang, and Kirmse, what can be concluded?

    a. Independent lung ventilation was not beneficial due to the patient's increased airway resistance.
    b. Independent lung ventilation resulted in cost-savings.
    c. High levels of PEEP dramatically decreased the patient's work of breathing.
    d. Independent lung ventilation greatly improved the patient's oxygenation.
    e. Independent lung ventilation should only be used in an operating room.

    [September 94:906-911]

12. According to cases reported by Thomas and others, exogenous surfactant therapy for ARDS due to aspiration of gastric contents has resulted in which of the following?

    a. improved oxygenation
    b. increased $P_{(A-a)O_2}$
    c. reduced dynamic compliance
    d. decreased lung volumes
    e. increased alveolar surface tension

    [September 94:912-916]

13. Which of the following statements is true about pulmonary artery catheterization in patients admitted to the hospital for COPD exacerbation, according to Smith and Pesce?

    a. Pulmonary artery catheterization is not cost effective.
    b. Pulmonary artery catheterization decreases morbidity and mortality.
    c. Pulmonary artery catheterization improves 5-year survival rates.
    d. This patient population demonstrates the highest incidence of sepsis, associated with pulmonary artery catheterization.
    e. Long-term quality of life dramatically improves for patients who undergo pulmonary-artery catheterization.

    [October 94:961-967]

14. Which of the following statements **is not** true about the caregiver education program instituted at Harborview Medical Center?

    a. Each nursing unit received an educational presentation on oxygen therapy during transport.
    b. Guidelines for oxygen use were posted on each nursing unit.
    c. A respiratory therapist was required to be present during all transports involving oxygen.
    d. Tables were posted, showing how to calculate the expected duration of cylinder oxygen.
    e. Memos were circulated to nursing units and the transportation department, stressing the importance of continuous oxygen therapy for hypoxemic patients.

    [October 94:968-972]

15. In Weber and associates' study performed on surfactant-deficient rabbits receiving high frequency oscillation, which %IT resulted in the largest tidal volume?

    a. 10%
    b. 14%
    c. 30%
    d. 50%
    e. 70%

    [October 94:973-978]

16. In the absence of auto-PEEP, what is the primary factor that determines the distribution of volume during mechanical ventilation?

    a. lung time constants
    b. lung compliance
    c. airways resistance
    d. ventilator mode
    e. chest-wall compliance

    [October 94:979-986]

17. The nomogram created by Chatburn and Anderson to predict blender settings required to deliver any CO_2-O_2 combination

    a. is useful in determining the PVR:SVR.
    b. is only valid when combinations of CO_2:O_2 are 10:90 or 5:95.
    c. is within 10% of CO_2 and O_2 values 99% of the time.
    d. is based on the technique described by Morray and Jobes.
    e. is within 1% of actual measured CO_2 values; and within 7% of actual measured O_2 values, 95% of the time.

    [November 94:1039-1046]

18. In adult asthmatic patients receiving albuterol, which aerosol holding chamber produces the best clinical response?

    a. Aerosol Cloud Enhancer
    b. Aerochamber spacer
    c. 100 mL of corrugated tubing
    d. Aerovent actuator amplifier
    e. the Aerosol Cloud Enhancer and the Aerochamber spacer functioned equally well

    [November 94:1047-1050]

19. In patients who present with soft tissue swelling accompanied by bleeding into the retropharyngeal space, the most appropriate initial intervention is

    a. suctioning.
    b. fiberoptic bronchoscopy to control bleeding.
    c. administration of racemic epinephrine.
    d. delivery of oxygen therapy.
    e. assurance of airway patency.

    [November 94:1051-1056]

20. According to a study by Mason, Miller, and Small, the Circulaire system of aerosol delivery

    a. exhibited greater extrapulmonary deposition than small-volume nebulizer aerosol delivery.
    b. reduced escape of the aerosol into the room by tenfold compared to small-volume nebulizer delivery.
    c. resulted in greater aerosol deposition in the lung than did small-volume nebulizers.
    d. did not show significantly greater lung deposition than small-volume nebulizers.
    e. produced an aerosol of significantly greater diameter than that produced by the conventional small-volume nebulizer.

    [December 94:1157-1161]

21. A bench model used by O'Riordan and associates to predict aerosol deposition during neonatal ventilation utilizes what type of aerosol-delivery system?

    a. small-volume ultrasonic
    b. small-volume pneumatic
    c. small particle aerosol generator (SPAG)
    d. metered-dose inhaler (MDI)
    e. large-volume pneumatic

    [December 94:1162-1168]

22. Risk factors for nosocomial pneumonia include **all but which** of the following?

    a. immunosuppression
    b. extremes of age
    c. underlying chronic lung disease
    d. prone positioning of patients
    e. immobilization due to illness or trauma

    [December 94:1191-1236]

23. According to a study by Torres and colleagues, which of the following methods of measuring volume during bias-flow ventilation is most accurate and associated with the fewest technical problems?

    a. addition of an in-line isolation valve
    b. open-circuit pneumotachograph attached directly to the ETT
    c. single pneumotachograph
    d. dual pneumotachographs
    e. triple pneumotachographs

    [January 95:22-27]

24. Which method of mechanical ventilation produces the least imposed work of breathing?

    a. Flow-triggering CPAP
    b. Pressure-triggering CPAP
    c. Flow-triggering PS
    d. Pressure-triggering PS
    e. None of the methods listed above produced a significant decrease in WOB.

    [January 95:28-34]

25. Which of the following statements about the safety module study reported by Lowe is true?

    a. Posttest results for students were not significantly better than pretest results.
    b. All groups demonstrated an improvement in posttest scores, following completion of the safety module.
    c. Respiratory care employees previously exposed to safety issues at other institutions demonstrated the greatest improvement from pretest to posttest.
    d. Data were collected over a 6-month period.
    e. Median improvement from pretest to posttest among all 3 groups tested was 50%.

    [January 95:35-38]

26. Which of the following statements about the asthma management program described by Lawrence **is not** true?

    a. Neither the partial nor full program participants had any hospital or emergency room visits in the year following intervention.
    b. The partial asthma-management program included peak-flow monitoring and action-plan instruction.
    c. The full asthma-management program included peak-flow monitoring and action-plan instruction, as well as 12 hours of additional instruction.
    d. Both the partial and full programs follow the Guidelines of the National Asthma Education Panel.
    e. Both the partial and full asthma management programs proved to be cost-effective.

    [January 95:39-43]

27. Which of the following statements **is not** true of cromolyn sodium?

    a. Cromolyn sodium is available in capsule form.
    b. Cromolyn sodium is available in nebulizer solution.
    c. Cromolyn sodium is available in metered-dose inhaler.
    d. It is associated with a low incidence of side effects.
    e. It should not be prescribed for children for prolonged periods.

    [January 95:108-113]

28. What measurement of lung function suggests which chronically ventilated preterm infant may have a negative response to inhaled bronchodilator therapy?

    a. FRC
    b. R_{tot}
    c. C_{dyn}
    d. V_T
    e. R_I

    [February 95:145-151]

29. What is the most common method of research instruction in advanced respiratory care practitioner education programs?

    a. formal courses in research
    b. journal studies
    c. reading research
    d. evaluating research
    e. conducting independent research

    [February 95:152-155]

30. Which method of oxygen enrichment to a portable volume ventilator **should not be** recommended, according to a study by McFalls?

    a. oxygen entrained into the air-inlet filter using an oxygen adapter with a 50-mL reservoir
    b. the manufacturer's oxygen-enrichment kit
    c. oxygen entrained into the air-inlet filter using an oxygen adapter
    d. oxygen bled into the circuit
    e. There was no clinically significant difference between any method listed above—they are all acceptable methods of oxygen enrichment.

    [February 95:156-161]

31. Which of the following did Shrake **not emphasize** as an important skill or knowledge area for the RCP to possess?

    a. computer literacy
    b. knowledge of the principles of managed care
    c. basic considerations of hospital finances
    d. contacts outside the respiratory care department
    e. adequacy of the physical plant

    [February 95:162-170]

32. Which of the following statements is true of the chest radiograph of a lung that is contused?

    a. The radiograph should be taken on full expiration to adequately visualize free air.
    b. The affected side may show a raised diaphragm.
    c. Well-defined lobar density is a common finding.
    d. The contused lung may appear smaller than the unaffected lung.
    e. The affected area appears as solid white, with visible fissures.

    [February 95:181-183]

33. When compared to physician-directed weaning, what is an outcome of respiratory-therapist-directed protocols for weaning cardiac patients from mechanical ventilation?

    a. an increase in patient complications
    b. fewer median total ventilation hours
    c. greater median total ventilation hours
    d. 100% of patients successfully weaned regardless of group
    e. More patients required reintubations in the therapist-directed-protocol group.

    [March 95:219-224]

34. According to Marini, weaning priorities include **all but which** of the following?

    a. Maintain an adequate FRC with PEEP of 3-5 cm H_2O.
    b. Minimize breathing workload with pressure support sufficient to overcome endotracheal tube resistance.
    c. Provide large tidal breaths at least once every minute.
    d. Gradually prolong T-piece trials.
    e. Administer CPAP.

    [March 95:233-238]

35. According to Sassoon and Mahutte, which of the following is true of flow-triggering?

    a. It imposes greater work of breathing than pressure-triggering.
    b. Base flow often produces high levels of PEEP.
    c. During weaning, it is more advantageous than pressure-triggering.
    d. Significantly greater patient effort is required to overcome intrinsic PEEP, compared to pressure-triggering.
    e. The patient initiates a breath while both the inhalation and exhalation valves are closed.

    [March 95:249-256]

36. Of the following factors, which one does not strongly affect a patient's ability to be weaned from mechanical ventilation?

    a. baseline functional status
    b. health status of other organs and systems
    c. duration of the patient's critical illness
    d. socioeconomic status
    e. duration of mechanical ventilation

    [March 95:263-270]

37. What is the most prevalent cognitive disorder among COPD patients in ICU receiving prolonged mechanical ventilation?

    a. short-term memory deficit
    b. language deficit
    c. long-term memory loss
    d. diminished ability to reason
    e. lack of orientation to place and time

    [March 95:277-281]

38. Which of the following statements **is not** true about the current advanced cardiac life support (ACLS) curriculum?

    a. Students must complete 9 case scenarios.
    b. Students must go through the CPR defibrillation station.
    c. Successful completion does not authorize the student to perform procedures that were learned during the course.
    d. Current ACLS courses have moved away from passive lectures toward interactive learning.
    e. Students must pass a written ACLS test.

    [April 95:338-345]

39. Regarding chest compression during cardiopulmonary resuscitation (CPR), which of the following **is not** true?

    a. The arms of the rescuer should be locked relatively straight.
    b. Abdominal compressions should be implemented as soon as possible.
    c. Compression rate should be 80-100/min.
    d. Compression duration should be around 50% of the total time of compression and decompression.
    e. Airway inflation should be used between chest compressions.

    [April 95:380-392]

40. Which of the following statements has been proposed by Pepe regarding ACLS?

    a. ACLS has been proven to be highly effective.
    b. ACLS has been shown to significantly increase survival rates for patients who are in ventricular fibrillation.
    c. ACLS has not been shown to be cost-effective.
    d. Early automated defibrillation should not be performed by first-responders.
    e. The number of ACLS courses should be increased nationwide.

    [April 95:427-436]

41. In the case reported by Milisch, Rho, and Schell, which of the following is true?

    a. Use of the closed-system suction catheter allowed for maintenance of the patient's ventilation and oxygenation.
    b. The patient was extubated, the suction catheter was removed, and the patient was successfully reintubated.
    c. Significant laryngeal damage occurred to the patient's airway.
    d. The practitioner advanced the catheter too far, causing the suction catheter to kink at the carina.
    e. The closed-system suction catheter actually perforated the wall of the patient's trachea.

    [April 95:438-440]

42. Of those discussed by Branson and Johannigman, which method of ventilation provides the most consistent tidal volumes, with the least amount of gastric insufflation?

    a. transport ventilator with a fixed flow
    b. bag-valve-mask ventilation
    c. mouth-to-mouth ventilation
    d. mouth-to-mask ventilation
    e. transport ventilator with an adjustable flow control

    [May 95:479-497]

43. Which of the following is true of do-not-resuscitate (DNR) policies?

    a. There has been an increase in the documentation of the rationale for withholding CPR.
    b. In only a few cases is the decision to withhold CPR made after admission to the hospital.
    c. Fewer than 50% of patients who die in the hospital have DNR orders.
    d. Patients are not required to receive information about advanced directives at the time of admission.
    e. Patients themselves participate in the vast majority of DNR decisions.

    [May 95:528-537]

44. The American Heart Association's (AHA) rationale for early defibrillation performed by first responders trained in BCLS includes **all but which** of the following?

    a. Ventricular fibrillation tends to deteriorate into asystole within a few minutes.
    b. Ventricular fibrillation is rarely seen in sudden cardiac arrest, so first responders would not encounter it often.
    c. Ventricular fibrillation of the heart has no pumping action.
    d. The probability of successful defibrillation diminishes rapidly over time.
    e. The most effective treatment for ventricular fibrillation is electrical defibrillation.

    [May 95:538-549]

45. Which of the following topics **is not** mandatory in the Pediatric Advanced Life Support course?

    a. emergency department delivery and resuscitation
    b. skill stations
    c. dysrhythmia recognition and management
    d. critical stress debriefing
    e. recognition of respiratory failure

    [May 95:575-587]

46. Which of the following is true of the face-shield CPR barrier devices evaluated by Simmons and associates?

    a. The Res-Cue Key face shield delivered the AHA's suggested tidal volumes.
    b. Back pressure of the Res-Cue Key face shield was the greatest of any of the face shields studied.
    c. Mouth-to-mouth rescue breathing delivered the greatest tidal volume.
    d. Mouth-to-mouth rescue breathing provided the greatest amount of back flow.
    e. Neither the face shields nor mouth-to-mouth breathing met AHA guidelines for acceptable tidal volumes during rescue breathing.

    [June 95:618-623]

47. Which of the following conclusions **was not** drawn by Buff and colleagues about circadian patterns of emergency asthma presentations?

    a. For all patients, emergency department visits peaked between 8:00 PM and 11:59 PM.
    b. For all patients, emergency department visits reached a low point between 4:00 AM and 7:59 AM.
    c. Adults most often presented to the emergency department in the late morning.
    d. Patterns of circadian rhythms were similar for all emergency department admissions, regardless of the diagnosis.
    e. Children most often presented to the emergency department between 8:00 PM and 11:59 PM.

    [June 95:624-630]

48. Which of the following is true about administration of aerosolized synthetic surfactant to dogs suffering from wood-smoke inhalation?

    a. Surfactant treatment dramatically improved P_{aO_2}.
    b. Hemodynamic values were not significantly different from dogs who received aerosolized saline.
    c. Surfactant-treated dogs exhibited a lower shunt fraction than saline-treated dogs.
    d. Synthetic surfactant is just as effective as natural surfactant in the treatment of smoke inhalation.
    e. The synthetic surfactant was acutely effective.

    [June 95:631-637]

49. **All but which** of the following represent 'new and improved' features of the Ciba Corning 840 blood gas analyzer?

    a. Peristaltic pumps have replaced vacuum pumps.
    b. The sample syringe is held in place by an automated aspiration assembly.
    c. A sampling device aspirates the precise blood volume necessary for analysis.
    d. Fiberoptic cables allow the user to view the blood sample during analysis.
    e. All of the above are new features of the Ciba Corning 840.

    [June 95:638-643]

50. Which of the following is true about cysteinyl leukotrienes?

    a. They mimic pathological changes seen in asthma.
    b. They cause bronchodilation.
    c. They decrease capillary permeability.
    d. Asthmatic patients are deficient in producing them.
    e. Therapeutic intervention has been aimed at increasing their production artificially.

    [June 95:655-657]

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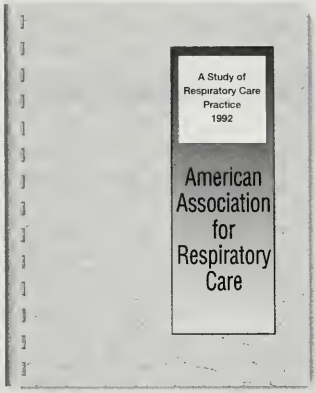

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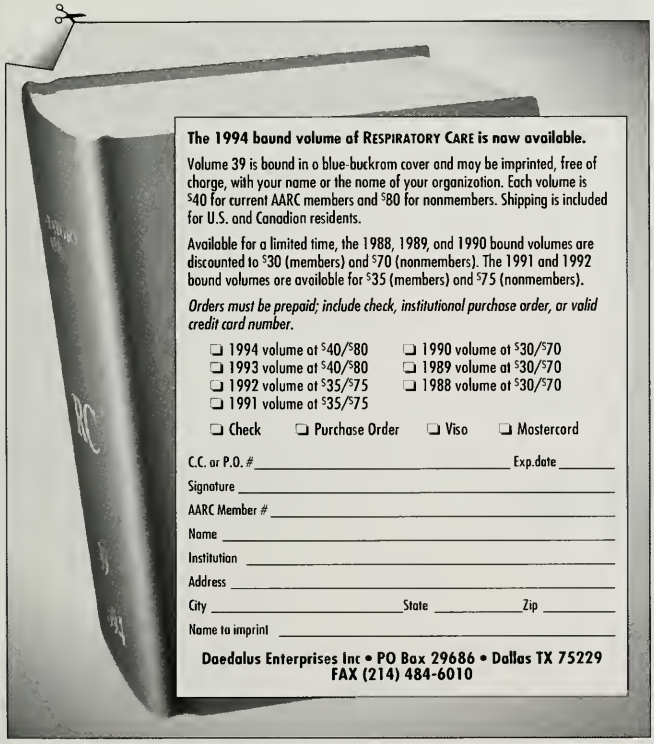

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THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only (RESP CARE)

Triage unit sequence #

A. Patient information

1. Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
___ lbs
or
___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ___ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ___

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ___

5. Expiration date (mo/day/yr)

6.
model # ___
catalog # ___
serial # ___
lot # ___
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

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FDA Form 3500 (6/93)

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Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

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- 1-800-822-7967 for a VAERS form for vaccines

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Calendar of Events

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August 23–25 in Albuquerque, New Mexico. The NMSRC presents its 29th Annual Convention "Sail the Caribbean," at the Albuquerque Convention Center. Health-care reform, respiratory care education, post acute care, bedside assessment techniques, and pressure-controlled ventilation are featured topics. Other events include a golf tournament, casino night, and Sputum Bowl. The meeting is approved for up to 9 CRCE Credit 1 hours. Contact Bill Oden at (505) 884-7721 or John Blewett at (505) 224-4138.

September 21–22 in Napa, California. Chapter 10 of the CSRC, the American Lung Association of the Redwood Empire and the respiratory therapy program at Napa Valley College present the 13th Annual Napa Valley Conference. Topics include therapist-driven protocols, primary care concerns in HIV, sleep-related breathing disorders, pediatric trauma triage, and ethics in ventilator termination. Contact Kate Benscoter at (707) 253-3145.

September 21–22 in Pittsburgh, Pennsylvania. The Southwest District of the PSRC announces the 22nd Annual Physiology and Medicine Meeting at the Sheraton Hotel, Station Square. Specialty tracts include management, nursing, and a new continuum-of-care tract. Contact St Francis Medical Center's Continuing Medical Education at (412) 622-4100.

September 26–27 in Honolulu, Hawaii. The HSRC and the American Lung Association of Hawaii host the 22nd Annual Respiratory Care Conference at the Hilton Hawaiian Village Hotel. Topics include treatment of airway obstruction by therapist-driven protocol, clinical trials in liquid ventilation, an update on high-frequency ventilation, newer forms of mechanical ventilation by protocol, and metabolic monitoring. Contact Wendell Inouye RRT, at Kapiolani Medical Center for Women and Children, (808) 973-8689, fax (808) 973-4730.

October 20 in Uniondale, New York. The Southeastern Chapter of the New York State Society for Respiratory Care hosts its 27th Annual Symposium at the Marriott Hotel. The symposium, "The Wheel of Change—Are We Prepared?" features a managers' breakfast, 50 exhibitor booths, and the annual awards luncheon. Contact Ralph Cavallo at (212) 523-3101 or Michael Karol at (718) 470-7680.

OTHER MEETINGS

September 15–17 in Kansas City, Missouri. The Missouri-Kansas Association of Cardiovascular and Pulmonary Rehabilitation announces its annual conference, entitled "Cardiac and Pulmonary Rehabilitation: Issues and Advancements," at the Holiday Inn Crowne Plaza. Participants can earn 9 CRCE Credit 1 hours. Contact Mary Cullen, RCP, at (816) 276-8711.

September 22-23 in Nagoya, Japan. The Asia-Pacific Association for Respiratory Care (APARC) presents its 4th Congress. A stellar international faculty addresses new modes of treatment and mechanical ventilation and the latest in patient management. For registration information and travel arrangements, contact Travel Plaza International Chubu Inc, Ishida Bldg 9F, 4-25-21 Meieki, Nakamura-ku, Nagoya 450, Japan. Phone: +81-52-561-9880/8655; Fax: +81-52-541-2520.

October 13 in Boise, Idaho. The Respiratory/Critical Care Section, VA Medical Center, and the John Butler Lung Foundation announce the 2nd Annual John Butler Lung Conference, a free 1-day symposium on recent advances in critical care medicine. Register early; seating is limited. CRCE credit has been requested. Contact Nola Darling at (208) 389-7956, fax (208) 338-7219.

October 19–20 in Fresno, California. The Respiratory Care Services Department of Valley Medical Center (VMC) and the Central Valley VMC Foundation present their 6th Annual Seminar and Equipment Fair, entitled "Controversies in Respiratory Care." Contact John Nausley or Karen Boswell at (209) 453-5197.

October 21 in Dearborn, Michigan. The University of Michigan Medical School Department of Internal Medicine announces its 1-day course, "Current Initiatives in the Care and Treatment of Asthma." The course's 3 objectives are to document current concepts of asthma pathogens, to give current perspectives on care of asthmatic patients, and to explain treatment with inflammatory drugs. Participants can earn 8 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association. Contact Registrar, Towsley Center for Continuing Medical Education, Department of Postgraduate Medicine and Health Care Professions, University of Michigan Medical School, PO Box 1157, Ann Arbor MI 48106-1157.

October 30–November 2 in San Antonio, Texas. The American Association of Homes and Services for the Aging (AAHSA) hosts its 34th Annual Meeting and Exposition – "Embrace the Power of Global Vision"– and offers 168 educational sessions, 4 general sessions, and an exposition of more than 350 companies. Call the AAHSA Annual Meeting Information Line at (202) 508-9400.

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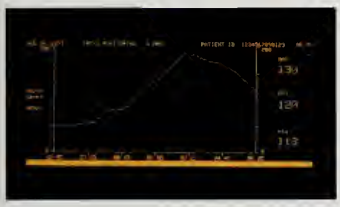

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